promising activity in neuroblastomas, medulloblastomas and rhabdomyosarcomas. A phase I study of CPT-11 is being conducted in children with recurrent or refractory solid tumors. CPT-11 is administered as a 120 mn i.v. infusion every 21 days, starting at 200 mg/m² dose level with a 20 % dose escalation. So far 12 patients (pts) have been enrolled on the first 4 levels. Their characteristics are : median age, 7.5 yr (10 months - 17 yr) ; sex ratio M/F, 9/3 ; PS (Lansky scale), 80 % (60-100) ; median number of previous CT lines, 3 (0-5). All the pts are evaluable for primary endpoint : dose limiting toxicity (DLT) determined at the first cycle.

Dose mg/m² (n)	200 (3)			240 (3)			300 (3)			350 (3)		
NCI-CTC Grade	0-2	3	4	0-2	3	4	0-2	3	4	0-2	3	4
Cholinergic Sd	3	0	0	3	0	0	3	0	0	3	0	0
ANC	2	1	0	3	0	0	2	1	0	2	1	0
Delayed diarrhea	3	0	0	3	0	0	3	0	0	3	0	0

Neither other limiting toxicity nor cumulative toxicity was observed through the 35 cycles administered. One minor response (glioma) and 5 stable diseases were observed among the 11 evaluable pts. A new cohort was recently open for heavily pretreated patients, i.e. prior high-dose CT and/or craniospinal irradiation : no DLT was observed in 3 pts at the first dose level. The total plasma clearance of CPT-11 ranged from 9.5 to 26.4 L/h/m² (mean ± SD, 16.4 ± 5.8 L/h/m²) as assayed by HPLC. Three metabolites, SN38, SN38-glucuronide and RPR121056, an oxidative metabolite, were present in the plasma and urine of all the patients. Conclusion : DLT is not yet achieved at the dose of 350 mg/m². Final results will be presented.

O-69

A study of the feasibility and accuracy of pharmacokinetically guided etoposide dosing in children.

Lowis SP, Pearson ADJ, Newell DR, Cole M
University of Newcastle upon Tyne

In the United Kingdom, at least 70% of children with malignant disease will receive etoposide-containing therapy. Etopside pharmacokinetics are highly variable between patients, up to 4-fold in children, and in adults have been shown to correlate with pharmacodynamic effects, most commonly acute haematological toxicity. Intra-patient variability is relatively small, and hence pharmaco-kinetically guided dosing (PGD) may lead to improved clinical effect.
methods. Nine children (6 male, 3 female) aged between 2y 2m and 18y 9m were studied following etoposide doses of 113 to 236 mg/m2. Only one patient had received prior cisplatin therapy. The area under the etoposide concentration-time curve (AUC) was estimated from a previously validated single sample method (Lowis et al, cancer res 54, 4881-4889, 1993) and dose adjustment made for the second day of treatment according to a defined target AUC.
Full pharmacokinetic studies were performed following the second etoposide dose, allowing the absolute error in exposure to be determined. Measurement of plasma etoposide with detailed pharmacokinetic sampling was by HPLC according to previously published methods.
Results. Pharmacokinetic parameters for etopside in these 9 patients were similar to previous data, but there was less inter-patient variability and a close correlation was seen between -37% and +18% were made. Target patient exposures were achieved with a high degree of precision and with little bias (ME and RMSE both 11%).
Conclusions. This is the first report of successfully targeted etoposide dosing following administration as a short infusion. Although the bias and precision achieved with this approach were comparable to that associated with conventional dosing, PGD may be of benefit in patients with abnormalities of renal or hepatic function, or with prior exposure to cisplatin.

O-70

INFANTS ACUTE LYMPHOBLASTIC LEUKEMIA CELLS ARE HIGHLY RESISTANT TO PREDNISOLONE AND ASPARAGINASE *IN VITRO* BUT HIGHLY SENSITIVE TO CYTOSINE ARABINOSIDE (AraC)

Pieters R[1], den Boer ML[1], Durian M[1], Janka G[2], Schmiegelow K[3], Kaspers GJL[1], van Wering ER[4], Veerman AJP[1,4]. Free Univ Hosp Amsterdam[1], COALL Study Group Hamburg[2], Univ Rigshospitalet Copenhagen[3], Dutch Childhood Leukemia Study Group (DCLSG) The Hague[4], The Netherlands.

Objective: The prognosis of infant ALL, characterised by a high incidence of the immature CD10⁻ negative B-lineage ALL (proB ALL) and MLL rearrangements, is poor. This study aims to determine the resistance profile of infant ALL cells.
Methods: *In vitro* drug resistance was determined by the MTT assay of 395 children with ALL at initial diagnosis: 21 infants < 1.5 yrs of which 9 were < 1 yr, 284 children 1.5-10 yrs (intermediate age group) and 90 children > 10 yrs. Phenotyping: 310 cALL/preB ALL, 69 T-ALL and 15 proB or prepreB ALL. Tested drugs: daunorubicin (DNR), doxorubicin (Dox), mitoxantrone, idarubicin (Ida), prednisolone (Pred), dexamethasone (DXM), vincristine, l-asparaginase (Asp), 6MP, 6TG, AraC, VM26 and 4-HOO-ifosfamide (4-HI). Statistics: MWU-test two-tailed, significance level 0.05.
Results: Infants < 1.5 yrs were significantly more resistant to Pred (median >500-fold), DXM (18-fold), Asp (11-fold) and VM26 (2.7-fold) but significantly more sensitive to AraC (2.4-fold) compared to the intermediate age group. When analysing infants < 1yr of age similar results were found except that these cases showed a trend for thiopurine resistance too. Children > 10 yrs were significantly more resistant to Pred (6.6-fold), DXM (3.7-fold), Asp (12-fold), Ida (2.1-fold) and 6MP (1.6-fold). ProB ALL cells were significantly more resistant to Pred (330-fold), DXM (39-fold), Asp (8.2-fold), and 1.6 to 4.2-fold to 6MP, 6TG, DNR, Dox and 4-HI compared to cALL/preB ALL but significantly more sensitive to AraC (2.3-fold). T-ALL cells showed a strong resistance to Pred, DXM and Asp and a mild (1.3 to 3.6-fold) significant resistance to all other drugs except thiopurines and VM26.
Conclusion: The poor prognosis of infant ALL is associated with a resistance to glucocorticoids and asparaginase. Of interest is the high sensitivity of infant ALL cells to AraC which supports the idea of using this drug more intensively in the treatment of infant ALL.

O-71

MODULATION OF ARA-C CYTOTOXICITY BY COADMINISTRATION WITH RIBONUCLEOTIDE REDUCTASE INHIBITORS AND ANTSIGNALLING DRUGS

J.Boos, A.Freund, C.Rössig, C.Lanvers, H.Jürgens, A.Gescher*
Dept. Pediat Hematology&Oncology, 48149 Münster FRG * MRC Toxicology Unit, University of Leicester, Leicester LE1 9HN, U.K

Objective: Ara-C has to be phosphorylated to the active metabolite ara-CTP which inhibits DNA polymerase and induces DNA strand breaks. Levels of ara-CTP are supposed to correlate with ara-C cytotoxicity and can be increased by combination with ribonucleotide reductase inhibitors. Combinations of ara-C with fludarabine (F-Ara-A) resp. cladribine (2-CdA) are presently under clinical evaluation. Ara-C also affects some cellular signal transduction pathways such as transcription/expression of c-fos, c-jun, NF kappaB, protein kinase C d, mitogen-activated protein kinase, cyclin E, cyclin-dependent-kinase-2 and retinoblastoma protein phosphorylation. These events may contribute to ara-C cytotoxicity. Antisignalling drugs like all-trans retinoic acid (ATRA) and bryostatin-1 are known enhancers of ara-C cytotoxicity.

Methods: We compared 7 antisignalling agents [ATRA and the kinase inhibitors quercetin, genistein, CGP 52411, tyrphostin A48, nordihydroguaiaretic acid (NDGA) and staurosporine] and 3 ribonucleotide reductase inhibitors [hydroxyurea (HU), F-Ara-A and 2-CdA] for their ara-C sensitising potencies. Cytotoxicity was assessed by the tetrazolium (MTT) assay in U937, HL-60 and newly-derived ara-C 1μM-resistant HL60/ara-C cells in at least three separate experiments. As mechanisms of interaction we measured the influence of selected modifiers on ara-CTP levels and cellular markers of apoptosis, i.e. cell size, DNA loss and DNA fragmentation.

Results: Sensitisation (= significant supraadditive cytotoxicity) was found in all cell lines for combinations of ara-C with HU or ATRA, and in neither of the cell lines for combinations with quercetin or genistein. CGP 52411 and tyrphostin A48 sensitised against ara-C in both HL60 cell lines, however counteracted in U937 cells. 2-CdA,

staurosporine and NDGA caused ara-C sensitisation in HL60 and U937 cells, F-Ara-A in HL60/ara-C and U937 cells. An increase of cytotoxicity was paralleled by an increase of cellular Ara-CTP with ribonucleotide reductase inhibitors and a decrease of Ara-CTP with ATRA.

Conclusion: Antisignalling drugs such as ATRA, NDGA, staurosporine, CGP 52411 and tyrphostin A48 might be efficacious alternatives to the already clinically applied ara-C modifiers. Increase of ara-CTP is not a precondition of modulation of ara-C cytotoxicity. Among the clinically used ara-C modifiers, HU sensitised more potently against ara-C than F-Ara-A and 2-CdA. (Supported by BMBF #01EC9401)

O-72

PHARMACODYNAMIC (PD) MODELING STUDIES OF CYTARABINE (ara-C) IN PEDIATRIC LEUKEMIA PATIENTS.

Clarke P. Anderson, Partha Nandy, Antonia Periclou, and Vassilios I. Avramis. Div. of Hema./Oncology, School of Medicine, Univ. of Southern California, Childrens Hospital Los Angeles, Los Angeles, CA 90027, U.S.A.

Considerable attention has been paid recently on the appropriateness of dose reduction of the antimetabolite drugs in infant patients with leukemia. The accepted modification of dosage of drugs, such as ara-C, and anthracyclines from dose per m² (surface area), to modified dose per kilogram of baby's body weight has worked without many problems, but the method is not based on prevailing pharmacokinetics rationale. In order to improve and provide a pharmacologically directed dose modification of the antimetabolite drugs like ara-C, we developed and reported a population pharmacokinetics model in pediatric patients (PPK) using NONMEM program (Periclou and Avramis, Cancer Chemother. Pharmacol. 39:42-50, 1996) and data from separate pediatric Phase I/II studies. The best model derived using the NONMEM program permitted us to identify AGE and SURFACE AREA as important covariate patients' parameters, which correlated with the clearance of ara-C, with a strong statistical value. We now have considered the equations for the non-compartmental modelling of ara-C in terms of drug dose adjusted for the clearance in its relation to patient's AGE and SURFACE AREA. These are: $Cl=DOSE/AUC_{0->\infty}$; and with the $Cl'=2.59xAGExSA$ l/hr, the equation becomes: $DOSE_{ADJ}$ = [(2.6) xAGExSA) x DOSE]/Cl. We solved these equations for ages 1 to 12 months by assuming that the Cl remains constant, and found that dose adjustments from 0.104x to 0.971x DOSE, should be done for children 1 to 9 months, respectively. For children, 10 months or older, this model suggests that no dose reduction is necessary. However, clinical experiences at CHLA have shown during a 4 year period that 5 pediatric patients less than 30 months (range 14-30 mo) of age have had interstitial pneumonitis after multiple course of ara-C 3-day infusions, not subjected to this model dose correction. Two of 5 patients died within 48 hours of symptomatology. The data suggest that this model provides us with a PD directed approach to reduce the ara-C dose in infants, but that this may have to be extended in clinical practice up to 2.5 years of age. The implications of this modeling are significant and may affect clinical outcome with ara-C. Clinical PD studies are planned in pediatric patients with leukemias to verify the model and answer these questions.

O-73

PHARMACOLOGY OF ARA-C GIVEN AS A CONTINUOUS INFUSION FOLLOWED BY MITOXANTRONE WITH AND WITHOUT AMSACRINE/ ETOPOSIDE AS RE-INDUCTION FOR RELAPSED OR REFRACTORY PEDIATRIC AML

M. F. Ozkaynak[1], M.D. , V. I. Avramis[2], Ph.D., S. Carcich[2], R.N., J. A. Ortega[2], M.D. [1]Dept of Peds, Sect of Hem/Onc, New York Medical College, Valhalla, NY; [2]Dept of Peds, Div of Hem/Onc, Childrens Hosp. of LA, Los Angeles, CA, USA

Four relapsed and eleven primary refractory pediatric acute myeloid leukemia (AML) patients were re-induced with a loading bolus of 0.5 g/m² ara-C followed immediately by a continuous infusion of ara-C (130 mg/m²/day) for 72 hours followed with four daily doses (12 mg/m²/day) of mitoxantrone (MTX). Eight of fifteen patients received an additional course of amsacrine and etoposide. Ten of fifteen (66%) achieved complete response (CR) and three partial response (PR) after ara-C/MTX. One patient died before disease assessment and one had no response after ara-C/MTX. The major toxicities seen during this therapy were infection and myelosuppression. Eleven of fifteen patients (73%) had documented life-threatening infections. Five patients died of infection, two of disseminated aspergillus, one of disseminated candidiasis, one of filamentous fungus (Acremonium) of lungs, and one of enterococcus sepsis/meningitis. Four of eleven life-threatening infections were caused by streptococci. For patients who received only ara-C/MTX, the mean and median time of duration of absolute neutrophil count of <500/mm³ were 28 and 29 days, respectively (range 17-37 days). The mean and median time of duration of platelet count of <50,000/mm³ were 43 and 52 days, respectively. Pharmacokinetic studies of ara-C and ara-U were performed in 13 of 15 patients. A steady state (C_{ss}) ara-c concentration was achieved at 2 hours after the bolus ara-C dose and was maintained up to 72 hours. The C_{ss} plasma concentrations of ara-C and ara-U averaged 10.33 +/- 0.81 uM and 139.14 +/- 17.8 uM, respectively. Also, pharmacodynamic studies of ara-CTP were performed on circulating leukemic cells from five patients. Four patients who had a significant increase ($p=0.0041$) in their C_{ss} ara-CTP concentrations achieved CR, whereas, one patient with an insignificant increase achieved a PR. Continuous infusion of ara-C followed by mitoxantrone is an active re-induction regimen in refractory or relapsed pediatric AML patients. The addition of amsacrine and etoposide did not improve the remission induction rate. Further studies are needed in a larger patient population to confirm these observations.

O-74

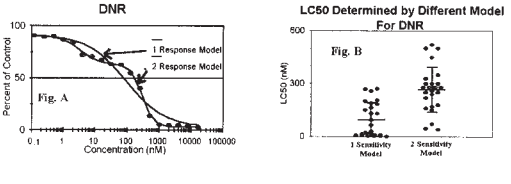
MTT ASSAY FOR ANTHRACYCLINES AND CYTARABINE IN ACUTE MYELOID LEUKEMIA: COMPARISION OF A TWO COMPARTMENT MODEL VS STANDARD METHODS FOR DETERMING THE LC50

Hamre MR, Simpson P, Buck S, Stout M, Ravindranath Y: Children's Hospital of Michigan, Barbara Ann Karmanos Cancer Institute, Wayne State University, Detroit, Michigan, USA

Objective: To determine if modeling of chemosensitivity curves by adapting the median effect method may distinguish different responses to an chemotherapeutic agent and provide better estimates of parameters such as LC50.

Methods: Mononuclear cells were isolated from AML samples and a suspension was prepared in media supplemented with 5637 bladder carcinoma cell line supernatant (a source of growth factors). Aliquots were placed in microtiter plates containing serial dilutions of DNR, AraC and mitoxantrone and in control wells containing no agent. At the end of incubation, MTT was added and the optical density was determined for each well, responses to drug were recorded as percent of controls. The curves were fitted utilizing an adaptation of the median effects equation to model for one or two distinct responses observed on the chemosensitivity curves.

Summary: For DNR and mitoxantrone 25/26 and 24/26 respectively, that the chemosensitivity curves were determined by using 2 types of sensitivities (Figure A). For the remaining patients and for AraC one type of sensitivity gave a good description. The LC50 determined by the two sensitivity model were higher than determined by the one sensitivity model for DNR (mean difference 171±153 nM, Figure B).



Conclusion: Chemosensitivity curves for anthracyclines display two distinct responses at different concentrations which affects the determination of LC50. Possible explanations could include cells with different drug sensitivities, *in vitro* effects of growth factors, cytostatic and cytotoxic responses, or different mechanisms of drug action.

O-75

ASPARAGINE SYNTHETASE IN PAEDIATRIC ACUTE LEUKEMIAS: A RATIONALE TO CONDUCT A PHASE II TRIAL WITH ASPARAGINASE IN AML-M5-SUBTYPE

A.Dübbers, P.Schulze-Westhoff, E.Kurzknabe, U.Creutzig, J. Ritter, G.Hempel, J. Boos
Department of Pediatric Hematology&Oncology, University of Münster,
48149 Münster, Albert-Schweitzer-Str.33, Germany

Objective: The enzyme L-asparaginase is used to achieve maximum reduction of L-asparagine in blood and CSF. Lack of sufficient cellular activity of asparagine synthetase in blast cells compared to normal tissues is thought to be the basis of the antileukemic effect in ALL. While L-Asparaginase is routinely used in acute lymphoblastic leukemia its role and value in the treatment of acute myeloblastic leukemia is still being discussed. As the drug causes a number of relevant side effects, the measuring the asparagine synthetase activity of individual patients´ blast cells might help to restrict the use to patients with low expression and to exclude others with high own synthetase capacity from this treatment. We, therefore, established asparagine synthetase monitoring.

Methods: Blast cells from patients are separated by Ficoll gradient centrifugation. Intracellular proteins (6000g-supernatant) are incubated in excess of required substrates and the synthesised asparagine levels then measured after 0,40,80,100 and 140 minutes (HPLC). The interassay coefficient of variation in several speciems is <20%. The activity is clculated as nM asparagine/mg cellular protein/hour)

Results:

	n	median (range)	mean±standard dev.
Non-T-ALL	13	11.7 (3.4-45)	15.5±12
T-ALL	5	8.6 (4.1-22.9)	10±7.5
AML (not M5)	18	12.6 (0.8-45.5)	16±12.8
AML-M5	9	3.8 (0.96-7.9)	3.9±2.2

There was no significant difference between myeloblastic and lymphoblastic leukemia. The observed activity was significantly lower in AML-M5 compared to the other myeloid leukemias ($p<0.005$, Mann Whitney rank sum test). T-ALL show a trend to lower activity compared to non-T-ALL.

Conclusion: AML and ALL, both show comparably low expression of asparagine synthetase with a wide range in both groups. The possible value of L-asparaginase in the treatment of AML should be reconsidered. We, therefore, initiated a multicenter trial to test the clinical activity in patients with relapsed AML-M5 and to determine the relationship between response to L-asparaginase treatment and cellular asparagine synthetase activity, mRNA expression (Dincalci, Milano) and in vitro asparaginase sensitivity (Pieters, Amsterdam). (supported by BMBF #01EC9401)

O-76

SAFETY AND EFFICACY OF L-LEUCOVORIN RESCUE ADMINISTRATION FOLLOWING HIGH DOSE METHOTREXATE THERAPY - PRELIMINARY RESULTS OF A CLINICAL AND PHARMACOKINETIC PILOT MULTICENTER STUDY

Ch Paál[1], Cs Csáki[1], T Ferencz[1], JR Kowalczyk[2], K Steel[3], and JD Borsi[1]
[1]2nd Dept. of Pediatrics Semmelweis Medical School, Budapest, Hungary [2]Dept. of Pediatrics Hematology, University Pediatric Hospital, Lublin, Poland, [3]Wyeth-Lederle, Austria

The efficacy of high dose methotrexate (HDMTX) therapy is influenced by the dose and duration of folinic acid (FA) rescue administration. The pharmacokinetics (pkx) of FA is characterized by major variability. In practice, however, it is only MTX serum levels that are monitored routinely. The determination of FA levels following the racemic d,l-leucovorin requires expensive, complicated laboratory techniques. The administration of l-leucovorin (l-leu) with HDMTX may make it possible to determine levels of MTX, l-FA and metabolites simultaneously. Our hypothesis is that this method could allow us to develop a pkx based treatment with HDMTX/FA in order to optimize therapy. At first, however, it was needed to be determined that l-leu can be used safely and effectively as a rescue agent. In the period of August 1994 to May 1996, 53 patients (10 children with osteosarcoma, 3 with NHL, 30 with ALL, 10 with medulloblastoma) entered the study and 204 treatment cycles have been analyzed according to GCP standards. All patients received HDMTX therapy as part of their respective chemotherapy protocol at a dose of 5-12g/m^2 during 6-24 hours following prehydration and alkalization. L-leu (Lederle, USA) was initiated at 30-42hrs following the start of MTX infusion at a dose of 7.5 mg/m^2 i.v. bolus. L-leu was repeated every 6 hours until serum MTX was < 0.2 umol/l. Venous blood samples were taken at the end of the MTX infusion, at 24 h, 48h, 72h following the start of MTX, or until serum MTX was < 0.2 umol/l. Samples were assayed for MTX with HPLC and frozen and stored at -20°C for later determination l-folate metabolites. Samples for complete blood count, UN, creatinine, electrolytes and transaminases before the administration of MTX, on Days 1 and 7 following MTX administration, or daily (as necessary) have been taken and analyzed. Statistical analysis of clinical and laboratory data obtained before and after treatment and at follow up has been performed, including the distribution analysis comprising calculation of means and SDs where applicable. Box and Whisker Plots of all values by patients and cycles and examination of MTX pkx in the elimination phase of the drug. All except 3 patients tolerated the HDMTX/L-leu therapy well and L-leu did not influence the pkx of MTX. There was only one adverse event possibly attributable to l-leu with a skin reaction. In conclusion, l-leu can be administered effectively and safely as a rescue agent with HDMTX therapy. In the next phase of the study we analyze leucovorin and metabolite concentrations with an HPLC method currently under development.

O-77

CYCLOSPORIN-A ENHANCES IFN-γ, IL-5 AND IL-13 PRODUCTION BY T CELLS COSTIMULATED THROUGH CD28

Stefaan W. Van Gool*° , Khadija Rafiq*, Ahmad Kasran*, Xiaohui Peng*, Penelope Brock°, Jan L. Ceuppens*
*Laboratory of Experimental Immunology, and ° Department of Pediatrics, Catholic University of Leuven, Leuven, Belgium

The CD80/CD86 - CD28 interaction provides a costimulatory signal for cyclosporin-A (CsA)-resistant IL-2 production and generation of CTL activity. The effect of CsA on CD28-costimulated Th1 and Th2 cytokine secretion is analysed. Anti-CD3 mAb was cross-linked on culture plates or on FcR-expressing P815 cells. A stimulating anti-CD28 mAb or CD80 (CD86), transfected into P815 cells, provided the costimulatory signal. IL-2, IL-4, IL-5, IL-10, IL-13 and IFN-γ were measured by ELISA. IL-2 production was hardly affected by CsA in these stimulating conditions. The productions of IL-4 and IL-10 were significantly blocked. The production of IFN-γ, IL-5 and IL-13 was markedly enhanced by CsA in the CD4(+) subpopulation. By using combinations of PMA/ionomycin/anti-CD3 together with CD28 costimulation, we could show that the effect of CsA on IL-5, IL-13 and IFN-γ production only occured when both intracellular calcium and CD28-mediated pathways were triggered. The decreased IL-10 production by CsA was responsible for the enhanced IL-5, IL-13 and IFN-γ production. The combination of CsA and IL-2(R) mAb completely blocked all cytokine production, demonstrating an important role of IL-2 for the production of Th1 and Th2 cytokines. In conclusion, CsA facilitates IFN-γ, IL-5 and IL-13 production by CD28-costimulated CD4(+) T cells. This suggests the existence of a negative regulatory signal which is calcium-dependent and probably IL-10-mediated. It also indicates different regulatory pathways for two groups of Th2 cytokines: IL-4 and IL-10 versus IL-13 and IL-5. This finding has major complications for immunosuppressive strategies based upon the use of CsA.

O-78

LACK OF TELOMERASE ACTIVITY IN IV-S NEUROBLASTOMAS

Willenbring H., Poremba C., Schäfer K.-L., Terpe H.-J., Jürgens, H., Böcker W., Dockhorn-Dworniczak, B. Gerhard-Domagk-Institute of Pathology & Department of Pediatric Hematology and Oncology, University of Münster, FRG.

Objective Treatment of neuroblastoma has remained a major challenge in pediatric oncology, the assessment of the individual prognosis in particular in disseminated disease is still obscure. Previous studies have correlated clinical outcome with activity levels of telomerase, a ribonucleoprotein which expression has been observed in a wide variety of malignant tumors.

Methods We analyzed 27 neuroblastomas of different clinical stages, including 16

IV-S neuroblastomas, 2 esthesioneuroblastomas and 2 ganglioneuromas employing a novel semiquantitative assay based on the detection of TRAP- products on an automated laser fluorescent sequencer (ALFexpress, Pharmacia).
Results Telomerase activity was detected in 13/27 tumor tissues. 15/16 IV-S neuroblastomas, both ganglioneuroma samples and 1 neuroblastoma sample after chemotherapy were negative for telomerase activity. Low telomerase activity was detected in only one IV-S neuroblastoma (histologically undifferentiated).
Conclusions Low or absent telomerase activity in IV-S neuroblastomas may be one explanation for eventual growth arrest and regression of tumor cells. Furthermore, telomerase activity may serve as a marker for therapy control in comparison of pre- and posttherapeutic samples. Analysis of TRAP-products on an automated laser fluorescence sequencer is a sensitive and specific method for semiquantitative detection of telomerase activity in tumor samples.

O-79

FAMILIAL WILMS TUMOUR IS GENETICALLY HETEROGENEOUS AND MAY INVOLVE THE *WT1* GENE

Pritchard-Jones K, King-Underwood L, Rahman N, Variend S* & Gerrard M*.
Institute of Cancer Research, Sutton Surrey & Sheffield Children's Hospital* UK.

At a genetic level familial Wilms tumour (WT) is heterogeneous and may be due to genes on chromosome 17q, 11p and elsewhere in the genome. A minority of familial cases are due to germline *WT1* gene mutations. Their identification will allow appropriate genetic counselling and screening.
Aims: Identification of patients likely to harbour germline *WT1* gene mutations.
Methods: *WT1* genomic sequence was analysed by direct sequencing of exons 1-10 amplified by PCR from both blood and fixed tumour DNA.
Results: In a study of 13 families with 2 or more cases of WT being analysed for genetic linkage to the *FWT1* gene locus on 17q12-21, one family was selected for *WT1* mutational analysis on the basis of clinicogenetic findings. Two siblings born of nonconsanguinous unaffected parents developed unilateral Wilms tumour. The daughter presented at the age of 2 yrs with a stage 3 tumour of fetal rhabdomyomatous type. She remains well 10 yrs later. Her brother presented at the age of 4 yrs with a stage 3 tumour showing biphasic histology (stromal and blastemal) with no evidence of anaplasia. He relapsed shortly after finishing standard treatment and subsequently died. He had severe bilateral cryptorchidism and hypospadias; genital surgery revealed persistent Mullerian structures in the presence of testicular tissue and a constitutional 46XY karyotype. Tumour karyotype showed an interstitial 11p13 deletion together with an extra isochromosome 1q. Sequence analysis of the *WT1* gene revealed that both siblings carried a germline 7bp deletion in exon 7 causing a frameshift and disruption of the zinc finger DNA binding domain. The mutation was inherited from their unaffected mother who had no obvious genitourinary abnormalities.
Conclusions: Germline *WT1* mutations are associated with more severe GU developmental abnormalities in the male than female and may be transmitted in familial WT. Both sporadic and familial cases with such features should be offered *WT1* mutational screening.

O-80

A PHASE I TRIAL OF CI-980 IN RECURRENT PEDIATRIC MALIGNANCIES: A PEDIATRIC ONCOLOGY GROUP STUDY (POG 9470)

Bernstein ML[1], Baruchel S, Devine S[1], Markoglou N[1], Wainer I[1], Vietti T.
[1]McGill University and the Pediatric Oncology Group

CI-980 is a novel synthetic tubulin binder which binds to the colchicine rather than the vinca binding site. Initial phase I trials in adults achieved a maximum tolerated dosage (MTD) of 4.35 mg/m^2/day, daily for 3 days, on a continuous intravenous infusion (CIVI) schedule. The dose-limiting toxicity (DLT) was neutropenia. Cortical toxicity (confusion and cerebellar dysfunction) was seen on this as well as on shorter infusion schedules. Patients (pts) were eligible for the POG trial if they met standard phase I criteria. Dosage levels investigated were: 3.5 mg, 4.2 mg, 5 mg and 6 mg, all CIVI daily for 3 days total. Granulocyte colony stimulating factor (G-CSF) was added after DLT neutropenia was reached. A total of 32 patients have been enrolled on study, 23 with extracranial solid tumors (ST), 9 with brain tumors (BT). The MTDs achieved (with DLTs seen at one dosage level higher) are: without G-CSF: 3.5 mg/m^2/day (DLT: neutropenia); with G-CSF: BT pts: 4.2 mg/m^2/day (DLT: myelosuppression: all pts. had received prior craniospinal irradiation; 2 more pts required for confirmation); ST pts: 5 mg/m^2/day (DLT: myelosuppression, cortical toxicity; 2 more pts required for confirmation). Response data will be presented when patient accrual has been completed. Pharmacokinetic data, using a new extraction and chromatographic method, showed a mean steady state level of 1.77 +/- 0.76 ng/ml, with a rapid decay after the termination of the infusion.

O-81

PHASE II STUDY OF VINORELBINE (VNR) IN CHILDREN AND ADOLESCENTS WITH REFRACTORY OR RECURRENT CANCER

Epelman S, Aguiar S, Silva A, Melaragno R, Nogueira M, Grande MT, Paula M.-
Department of Oncology, Centro Infantil D Boldrini. Campinas. Brazil

The development of effective new agents for children with cancer is crucial. Vinorelbine is a unique semi-synthetic vinca alkaloid synthesized from catharanthine and vindoline extracted from vinca rosea leaves. VNR differs from other vincas in that caranthine ring rather than the vindoline ring is modified. This structural change imparts pharmacologic properties which may translate into clinical benefits in the treatment of human cancer. Adult phase I studies have determined a MTD of 30 mg/m2mweek. We initiated a phase II study to evaluate the response and toxicity in children and adolescents. Twelve children (age 2 to 16 years - median 12 years) with refractory or recurrent cancer were entered in this study. All pts had measurable disease and signed a informed consent. 8 pts had recurrent disease while on therapy. VNR was administered at 30 mg/m2/week as a weekly out patient infusion for 4 cycles through a newty accessed peripheral vein. To date 8 pts are evaluable for response and toxicity. After 4 cycles: 3 pts showed a partial response (1 Wilms´, 1 Hodgkin`s disease and 1 rhabdomiosarcoma), 1pts had stable disease (adrenal carcinoma) and 4 pts showed progressive disease (2 osteosarcomas, 1 Ewing´s sarcoma and 1 medulloblastoma). Toxicity was analyzed after 40 cycles, leucopenia grade 3 according WHO criteria was encountered in 5 cycles (11%) after 3rd or 4th course. No neurotoxicity was observed . Five pts developed cutaneous toxicity grade 3. No life-threatening adverse effects were reported. Preliminary data suggests that VNR as utilized seems well tolerated. Partial response was achieved in 35 % of the pts. Patients are continue to enter into thi study to further determine the efficacy and safety of this drug.

O-82

PROTECTION OF PROXIMAL TUBULAR CELLS BY ETHIOL (AMIFOSTIN) IN IFOSFAMIDE CONTAINING REGIMENS.

J.de Kraker, M.Bierings, N.Langeveld, P.A.Voûte
Emma Kinderziekenhuis/AMC, Dept. Paediatric Oncology
Amsterdam, the Netherlands

Toxic effects on normal tissue is often dose limiting in chemotherapy. In paediatric oncology nephrotoxicity as a consequence of ifosfamide (IF) therapy is a well known limiting factor to the use of this drug. Ethyol (amifostine) is an aminothiol with cytoprotective characteristics to various normal tissues. Data in adult patients with ovarian cancer receiving anticancer drugs indicate among others that amifostine can reduce nephrotoxicity without interfering with the antitumour activity. We studied this property in sarcoma patients receiving ifosfamide containing regimens.

Patients and methods: In 8 patients (3 rhabdomyosarcoma, 5 Ewingsarcoma) aminoaciduria, fosfate reabsorption (TRP) $ß_2$ microglobulin ($ß_2$-m) excretion and 99m Tc-dimercaptosuccinic acid (DMSA) renal scintigraphy were performed prior to therapy and within 72 hours after the second course of IF. The total dose at that time was 12gr/m^2 of IF. Four patients received amifostine prior to and during the IF infusion. The amifostin dose was 740 mg/m^2 15' prior to and again 2 hours after initiating the IF infusion which ran for 3 hours.

Results: The mean age of the protected group was 9 $^4/_{12}$ years, in the control group 12 $^2/_{12}$ yrs. All values for TRP were normal prior and after IF. Aminoaciduria was also not different before and after therapy in both groups. $ß_2$-m excretion in a morning sample was normal in all patients prior to therapy. After therapy the mean excretion in the amifostine was 12,8 and 4,7 mg/ml in the control group. Mean DMSA-uptake decreased in the control group from 38% to 20% and in the amifostine from 38% to 23%.

In conclusion: After a cumulative dose of 12gr/m^2 of IF TRP and nitrosurea excretion are of no practical value even if studied very short after the IF administration. $ß_2$-m excretion and DMSA scintigraphy are valuable tools. In this study we found no evidence for protection of the tubulotoxicity of IF by amifostine but the numbers are small, the cumulative dose of IF low and one could be critical concerning the observation time.

O-83

PRELIMINARY RESULTS OF A NEW GENERATION URATE OXIDASE ENZYME, SR 29142 , FOR PREVENTION AND TREATMENT OF HYPER-URICEMIA RELATED TO TUMOR LYSIS SYNDROME IN CHILDHOOD ACUTE LEUKEMIA (AL).

Landman-Parker J[1], Auvrignon-Decubber A[1], Tourniaire B[1], Le Cosquer AC[1], Thioulouse E[1], Menard I[1], Nomdedeu S[1], Tabone MD[1], Dollfus C[1], Adam M[1], Lascombes F[2], Job B[3], Leverger G[1]. [1]Armand-Trousseau Children's hospital, Paris, France, [2]Sanofi, Nancy, France, [3] Sanofi, Gentilly, France.

Introduction : In most mammals, the final step of purine catabolic pathway is allantoin, as a result of transformation of uric acid into allantoin by urate oxidase, an enzyme which does not exist in man. Allantoin is a highly soluble product compared to uric acid, and is easily excreted by the kidneys. In order to prevent hyperuricemia secondary to chemotherapy and acute renal failure due to hyperuricemia, a second generation urate oxidase enzyme, SR 29142 (SR), produced by a genetically modified yeast strain, is now being developed by Sanofi. Animal studies have demonstrated the absence of any toxic effect of SR. In healthy volunteers, SR produced rapid and marked fall in plasma uric acid levels as early as 2 hours after dosing. SR is currently beeing evaluated in patients during induction chemotherapy for acute leukemia (AL)or non-Hodgkin lymphomas in open label phase 2 studies.

Patients : In our unit, 35 children, 2.3 to 15.9 years old (m=6.4), with newly diagnosed AL were included beetween 03/96 and 01/97. Median leukocytosis was 28.700 WBC/mm3 (1-221.000) and and median initial uric acid level was 272 µmoles/l (105-712)(Nl<420).

Methods : SR is daily administered as a 30 mn infusion in a saline solution at the dose of 0,15 mg/kg/day for 5 to 7 days and was started 24 to 48 hours before the beginning of chemotherapy in association with hyperhydration.

Résults : The mean uric acid level dropped dramatically by about 95 % 4 hours after the first infusion, and a very low level was maintained up to 24 hours after the last one. In 1 patient with bulky disease, an early lysis syndrome occured, resulting at H24 in a very transient hyperuricemia (uricemia normalized at H36 and thereafter). In only 1/35 pts, SR had to be stopped after transient grade 1 cutaneous allergic reaction. As expected, renal function remained normal in all the patients as evidenced by creatinine plasma concentrations during treatment by SR.

Conclusion : According to these preliminary results, SR appears to be a well-tolerated fast acting and highly potent uricolytic agent useful in prophylaxis and treatment of hyperuricemia related to tumor lysis syndrom.

O-84

Quality control of radiation therapy in medulloblastoma
(French Society of Pediatric Oncology)

C.Carrie[1], V.Moncho[2], JL Habrand[3], S.Hoffstetter[4], C.Alapetite[5], JP Maire[6], JL Lagrange[7], M Benhassel[8], X Muracciole[9], A Pons[10], F Doz[5]

1Centre Léon Berard,Lyon -2Centre Oscar Lambret,Lille -3Institut Gustave Roussy,Villejuif -4Centre Alexis Vautrin,Nancy -5Institut Curie,Paris -6Hôpital Saint André,Bordeaux -7Centre Antoine Lacassagne,Nice -8Centre Eugène Marquis,Renne -9Hôpital La Timone,Marseille -10Centre Claudius Regaud,Toulouse -

Methods : 113 children with medulloblastoma were included in two prospective studies (SFOP) for localized (74) or metastatic (39) medulloblastoma. A panel of radiation oncologists reviewed the dose prescription, dose distribution, port films according to preestablished guidelines. Protocol violations were registered as minor of major deviations according the predefined rules. In case of relapse a scheme of the precise site was recorded by the physician. The existence of a correlation between the protocol deviations and the site of relapses was investigated.

Results : In the 113 enrolled patients, 85 had a least one deviation of balistic (30 major deviations and 52with only minor deviations). In addition, in 3 cases the choice of energy for electron beam was considered as inadequate. Deviation in dose prescription was observed in 9 cases (range : lack of 5,4 Gray to 11 Gray in excess). 25 patients had no deviation either in balistic or in dose prescription. Thirty two relapses occured. The relapse rate was 20% in patients without procole deviation and 33% in those having at least 1 deviation. Two ou of the three patients who had eye block protocol deviation developed frontal recurrences.

Conclusion : Quality control of radiation therapy is an important issue in the analysis of medulloblastoma outcome. Treatment failures can be related to inadequate technics of radiation therapy. A prospective control is necessary and could be possibly performed using visual data through a computerized network..

O-85

RELAPSE ANALYSIS FOLLOWING COMBINED CHEMOTHERAPY (CT) AND LOW DOSE RADIOTHERAPY (RT) IN CHILDHOOD HODGKINS' DISEASE

G. Sotti, G. Frezza, G. Scarzello, R. Burnelli and V. Vecchi for the Italian Association of Pediatric Hematology and Oncology.

From February 1989 to February 1996, 273 pts were entered in the Italian Hodgkins' Disease Study AIEOP-MH'89-CNR protocol. The characteristics of the 257 evaluable pts were as follows: 166 males and 91 females (M/F=1.8), mean age 11yrs (1-15). Histologic patterns

were: NS 171, LP 25, MC 53, LD 4, NC 4. Regarding stage distribution, 46 were IA, 4 IB, 73 IIA, 31 IIB, 53 IIIA, 19 IIIB, 13 IVA and 18 IVB. Pts were divided into 3 groups according to clinical stage and mediastinal mass: Group 1 (100 pts in stage I and IIA ± M/T < 0.33) was treated with 3 ABVD courses plus IF-RT 20 Gy. Group 2 (107 pts in stage IEA, IB, IEB, I-IIA with M/T > 0.33, IIEA, IIB, IISA, IIEB, IIIA) received 6 cycles of alternating MOPP-ABVD plus IF-RT. Group 3 (50 pts in stage IIIB and IV) was treated according to SIOP protocol HD-87. Among the 257 pts from this study, 3 relapsed during CT and 18 after first complete remission (1/4 IB, 5/73IIA, 5/31 IIB, 3/53 IIIA, 3/19 IIIB, 4/18 IVB). The median time from diagnosis to relapse was 18 months (2-67). The most frequent site of relapse was mediastinum in 12/18 pts. 8 of these presented large mediastinal mass at diagnosis (8/74). 4 other pts relapsed in subdiaphragmatic sites initially uninvolved. 13/18 relapsed in irradiated sites. 8 pts are alive in II CR, 2 in III CR, 3 alive with disease, 1 still in therapy and 1 lost to FU. In conclusion few pts (8%) relapsed after combined CT and low dose RT. Half of these pts can be cured.

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O-86

EXPERIENCE WITH HYPERFRACTIONATED RADIOTHERAPY (HFRT) IN THE CURATIVE MANAGEMENT OF NEUROBLASTOMA (NB)

O Dupuis[1], JL Habrand[1], S Helfre[3], O Hartmann[2]. Depts of Radiations[1] and Pediatrics[2], Institut Gustave Roussy, Villejuif and Dept of Radiations[3] Centre Léon Bérard, Lyon, France.

One of the objectives of hyperfractionation in radiotherapy is to limit long term sequelae when total dose is kept constant. From July 1989 through March 1995, 29 children underwent HFRT (BID). Mean age was 38.4 months (range 3-103) with only 1 patient under 12 months, and M/F sex ratio 1. Initial primary was abdominal in 28 and pelvic in 1. Ten children had limited disease at presentation (stage II = 1, stage III = 9) while 19 had disseminated disease (stage IVs = 1, stage IV = 18). Nmyc expression was assessed in 17 of the latest patients and was found amplified in 13. Initial therapy consisted in induction chemotherapy (CAdO = CPM, ADM, VCR ; VP16 + CDDP or carboplatine) 4-8 cycles, followed by resection of the primary and regional lymphatic drainage. The patient with stage II Nb had primary total tumor resection and no chemotherapy. One patient was inoperable for medical reason. Intensive chemotherapy with autologous or allogenous BMT was conducted in children with metastatic disease. HFRT was administered for gross residual disease in most patients (= 22) or microscopic disease with Nmyc amplification (= 7). Three patients were in local progression before initiation of radiotherapy. Target volume varied throughout the time (postoperative or preoperative tumor volume). Total dose was adapted to the children's age and extension of the disease and 30-35 Gy were generally delivered (range 20-40). Two daily fractions of 1 Gy (range 0.8, 1) with at least a 6 hours intervall were delivered 5 days a week using 4.5 MV X-rays (28), 18 MV X-rays (1). Gastrointestinal toxicity was very limited and few children experienced mild thombopenia, all of whom had receive intensive chemotherapy before. With a median follow-up of 37 months (range 23-74), 16 children are alive of whom 13 in CR, 1 in both local and distant progression and 2 with distant metastases. Eight patients (27,5%) failed loco-regionally : 4 (13,7%) in field, 3 marginally and 1 outside the fields. When Nmyc was amplified, local failure rate was 4/13 (in field = 3). These results can be compared to those of 37 children treated earlier at our institution with conventional fractionation RT and of whom7 failed locally (in field = 5). This population presented more limited disease with 62% stage II-III. We conclude that HFRT is probably as effective as conventional RT if the treated volume encompasses the preoperative residual disease. A longer follow-up will tell if HFRT reduces effectively the late morbidity in these children.

O-87

GAMMA KNIFE IN CHILDHOOD GLIAL BRAIN TUMORS

Amendola,B.E., MD., Wolf,A.L.,MD., Coy,R.S.,Ph.D., Schwade,J.G.,MD.,Godinez,J.MD.Mount Sinai Cancer Center and HealthSouth Doctors Hospital. Coral Gables,USA.

Classically, Gamma knife radiosurgery has been used in small arteriovenous malformations and tumors. Careful treatment planning with multiple isocenters using Magnetic Resonance imaging (MRI), Magnetic Resonance Angiography (MRA), Computed Tomography (CT), and improved treatment planning software allowed for treatment of large tumors in the pediatric age group.

From November of 1993 to November of 1996 twenty-seven children with brain tumors were treated by radiosurgery . Of these, seventeen were of glial origin. There were seven astrocytomas, four glioblastomas, two optic nerve gliomas, two oligodendrogliomas and one brain stem glioma. Dosage given varied from twelve Gy to twenty Gy to the 50% isodose line. Three patients required two treatments.

Astrocytomas did better with excellent local control and minimal side effects. Two GBM patients survived more than one year from radiosurgery.

Twelve patients are alive and without evidence of disease, NED, with survivals ranging from three to thirty six months. Although follow up is short, the results are promising.

O-88

BRACHYTHERAPY (BT) IN THE INITIAL MANAGEMENT OF SOFT TISSUE SARCOMAS IN CHILDREN. UPDATE OF THE MMT 89 SIOP STUDY.

J.L. HABRAND, M.A. COULON, C. HAIE-MEDER, F. OLDENBURGER, D. SPOONER, O. OBERLIN, Institut Gustave Roussy, Villejuif (France), MC University, Amsterdam (Holland), and SIOP MMT Committee

Between January 1989 and May 1995, 23 children and adolescents who were part of the MMT 89 protocol received BT as part of their initial management. This represented only 6 % of the irradiated patients. Mean age was 3.5 years (4 months - 13 years), M/F sex ratio was 1.5. Pelvis was mainly concerned : 15 cases (bladder 8, vagina 4, para rectal 1, prostate 1 NA 1), then head and neck : 8 cases (orbit 2, others 6 including 3 para meningeal).

Staging according to the SIOP classifications was T1 : 12, T2 : 11. N1 was present in 7. All tumors were of the rhabdomyosarcoma type. Management consisted in an initial chemotherapy (CT) regimen (generally IVA : Ifosfamide, Vincristine, Actinomycin D, 6 courses ± 2nd line) followed by a surgical exploration. This allowed an ovarian transposition in the pelvic sites, assessment of the post CT status and, in 17 children, a conservative resection. Only 2 children required an extensive resection including 1 non responder to CT. Low dose rate iridium 192 was employed in all patients in interstitial implants (13) or endocavitary procedure (10). Total dose ranged between 20 and 65 Gy (mean 49) given alone or in combination with external beam (2)

With a median follow-up of 34 months (range 9 - 81), 69 % of children (16/23) are alive and with NED. 5/23 (22 %) have presented a local regional

failure (LRF) within 2 years (med 10 m) and 2 a metastatic evolution : patients at risk for LRF were head and neck (3), bladder (2) and N1 (4). BT represents a valuable radiotherapeutic technique in expert hands that allowed organ preservations in highly "sensitive" sites such as orbit or pelvis (only 1 salvage hysterectomy).

O-89

LOCAL CONTROL AND TOXICITY OF HYPERFRACTIONATED ACCELERATED RADIOTHERAPY (3 FRACTION/DAY) FOR IRS-GROUP III RHABDOMYOSARCOMA (RMSA).

L. Gandola, F. Lombardi, G. Cefalo, M. C. Gianni, R. Luksch, M. Massimino, P. Navarria, R. Kenda, F. Fossati-Bellani.
Istituto Nazionale Tumori, Milano, Italy

Objective. In the attempt to increase treatment intensity, improve local control, and reduce late sequaele, we have treated children with unresectable or partially resected RMSA with hyperfractionated-accelerated radiotherapy (HART) as a part of a combined modality treatment .
Patients. From 2/89 to 5/94, 28 consecutive pts (M 17, F 11; median age 7,6 yrs, range 3-18 yrs; embryonal 19, alveolar 8, unclassified 1) entered the study, after biopsy alone (19 pts) or partial resection (9 pts). Primary tumor sites were: head-neck 18 (parameningeal 11/18), pelvis 3, paratesticular 3, retroperitoneum 2, limbs 2.The first 18 pts received primary CT with alternated ADM, ACTD, CTX, VCR for 8 weeks while the remaining 10 pts received the same drugs at higher doses plus high-dose CTX for 13 weeks. HART was administered in 3 daily fractions (1.5 Gy/fraction) at 5-hr intervals to a total dose of 49.5 Gy in the first 18 pts and of 54 Gy in the remaining 10 over 11-12 days respectively (weekend excluded). Maintenance CT was administered with the same 4 drugs for 9 mos in the first group and with IFO, VP16 and high-dose CTX over 3 mos in the second group.
Results. Primary CT induced a CR in 22% of pts and a PR in 74 %. HART induced a CR in 9/18 (50%) evaluable pts, and improved PR in 6 (30%), while in 3 pts disease remained stable. At the end of maintenance CT, twenty of 28 pts (71%) were in CR. Twelve of 28 pts (43%) are alive in CCR after a median of 72 mos (43-90 mos); 8 (28%) relapsed at primary site inside HART fields after a median of 16 mos (7-24mos); 7 (25%) developed distant metastases after a median of 9 mos (3-16 mos).Relapse rates were comparable in the two treatment groups.One pt is alive in 2nd CR 68 mos from local relapse, and 1 pt died in PR for a suspected brain-stem radionecrosis (+8mos).The only relevant HART acute side effect was a necrotizing oropharyngeal mucositis in pts with head-neck primary, that required a radiotherapy split (13 days) in only 1 pt, but a maintenance CT delay of 2-10 weeks in 9 pts. Four severe late sequaele occurred:1 suspected brain-stem radionecrosis, 1 second malignant tumor in the irradiated volume (+47 mos from HART), 2 orbital exenterations.
Conclusions.The therapeutic index of our intensive combined treatment is unsatisfactory.In particular, HART did not increase local control of IRS-Group III RMSA as compared to conventional RT.Results will be analyzed based on prognostic factors as patient age, primary site and disease extent at diagnoses.

O-199

LONG TERM EFFECTS OF CHILDHOOD CANCER AND QUALITY OF LIFE - THE STATE OF ART IN EUROPE-

Gabriele Calaminus, Gwendoline Kiebert
EORTC Data Center, Brussels, Belgium

Introduction: Since more and more children survive a childhood malignancy, the long term effects of treatment become increasingly important. Different activities are initiated in European pediatric oncology studies to estimate these effects. We performed a survey of all ongoing activities in Europe as well as a literature review of studies that report on these issues and on quality of life (QoL).
53 pediatric oncology study groups, responsible for treatment of all different childhood cancers, were contacted by questionnaire to evaluate, if studies on long term effects are initiated or planned with respect to the different diseases. As in some European countries late effect study groups have already been established, these groups were contacted as well for evaluation.
Results:At present the UK, Italy, Germany, Spain, the Netherlands and the nordic countries are collecting data on long term effects of treatment in childhood cancer survivors on a national base.
The covered areas are: long term effects on cognitive functioning, growth, fertility and organ functions (ear, heart, lung, kidney), data about secondary malignancies are collected as well, mainly focussing on long term survivors of: childhood leucemia, solid tumors and brain tumors. Data on QoL are not measured systematically in these studies.
Regarding the published data on QoL which represent mainly institutional experiences, a high variety of measurement instruments, target groups and covered QoL domains are identified. 68 publications where evaluated. The covered variables are: body image, cognitive functioning and educational achievement.The time of examination is not standardized in most of the studies.
Conclusions:We could detect a large variety of between and in studies, which focus on long term effects and QoL.This leads to the problem of incomparability and unrepresentative results. So we suggest: a). a standardized methodology of assessment, b).a collaboration at a European level, c). the conduction of specific studies evaluating long term effects and QoL.
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O-90

INDEPENDENT ADULT FUNCTIONING IN SURVIVORS OF CHILDHOOD ACUTE LYMPHOBLASTIC LEUKAEMIA (ALL) AND WILMS ' TUMOUR.

MACKIE EJ. KONDRYN H.# EDEN OB.# HILL J ***
**Southampton Gen Hosp#ChristieHosp Manchester **Royal Liverpool Children's Hosp, UK*

OBJECTIVE : As survival rates continue to improve in childhood cancer, increasing attention is being directed at the long term sequelae of treatment. This study addressed the psychosocial outcome of adult survivors, specifically examining independent adult functioning and interpersonal relationships.
METHOD : All subjects aged 19-30 years, surviving either ALL or Wilms' tumour and 5 years out of therapy were recruited from the Manchester Tumour Registry. Adult functioning was assessed using the ADAPFA (Adult and Adolescent Personality Functioning Assessment), an investigator-based interview, examining interpersonal functioning in the domains of Work, Love Relationships, Friendships, Non specific social contacts (NSSC), Negotiating skills and Coping. An interview to explore the effect of cancer on these domains was also administered.
RESULTS : Preliminary data is available on 79 subjects (ALL=52, Wilms'=27) and 72 controls (sex, age and geographically matched). Anovas for the three groups were significant at $p < 0.01$ in the domains most reliant on the development of interpersonal skills ie love relationships, NSSC and friendships. These findings were accounted for using t-tests, which demonstrated dysfunction in survivors of ALL when compared to both survivors of Wilms' and the control group. These difficulties were present through adolescence into early adult life (each subject was rated in two time periods, 16-20 years and 21-25 years). No significant differences between the two survivor groups and the controls were found in the domains of work, negotiating skills and coping. Significantly more surviving ALL compared to Wilms' tumour perceived that their illness had produced a negative effect on schooling ($p=0.001$), but not on employment. Forty-eight per cent of all subjects felt that the effect of the cancer had hindered their love relationships in some way.
COMMENT: Young adult survivors of ALL demonstrate significant dysfunction in the areas of their life, which require well developed interpersonal skills. The implications of these findings for future research and long term follow up will be discussed.

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O-91

MUSIC THERAPY IN A PAEDIATRIC ONCOLOGY SETTING

I. Bracke, T. Vercruysse, K. Jennes, S. Van Gool, A. Uyttebroeck, P. Brock, M. Casteels-Van Daele. Dept. of Paediatrics, University Hospital, Catholic University of Leuven, Belgium.

Music therapy is a psychodynamic treatment method. Psychological problems and conflicts can be worked through by the use of music as a therapeutical medium. Over the last 40 yrs music therapy has been particularly applied to physically and mentally handicapped patients as well as being used in psychiatrics units.
Since October 1990 music therapy has formed part of the psychosocial support of cancer patients at our hospital. The music therapy is offered by a trained music therapist. The aim of music therapy is to give the children a broad and child-based range of opportunities to help cope with their illness and treatment. Individual music therapy is offered particularly to the hospitalised patients where specific musictherapeutical techniques are used. In the initial fase from January 1991 to December 1996 we observed a group of 203 frequently hospitalised patients to whom music therapy was offered. Of the group of 203 patients : 23 children refused music therapy sessions; 23 patients took part in only a few sessions and did not want to continue; 157 patients took part in the sessions on regular basis (2 to 4 times a week during their hospitalisation). Of these 157, 95 enjoyed playing music in a recreative way with little psychotherapeutical involvement of the music therapist, whereas in 62 patients of the music therapy played an important role and a real psychotherapeutic effect. These children used the music therapy to cope with their uncertainty, loss of control, negative feelings and threat to their self-image. We noticed that a number of these children had poor verbal communication skills. For these children the nonverbal symbolic aspect of music is significant. In conclusion, music therapy has a place in the psychosocial support of children with cancer.

O-92

THE EVALUATION OF PARENTS' SATISFACTION: THE AUDIO-TAPING OF THE COMMUNICATION OF DIAGNOSIS AS EXAMPLE.

G.Masera, A.Corbetta, D.Fraschini, L.Adamoli and M.Jankovic - Pediatric Clinic, University of Milan, S.Gerardo Hospital, Monza, Italy

Objective: To present a "critical" analysis of parents' point of view in order to evaluate one aspect of the psycho-social interventions: the communication of diagnosis of leukemia.
Methods: To the parents the possibility to register the communication of diagnosis of leukemia including the complete "project of care", present both parents, the Director and the family doctor, was offered. This procedure is made a short time after a preliminary communication made in the first days. Since January 1995 in 63 consecutively diagnosed children (58 Acute Lymphoblastic Leukemia, 5 Acute Myeloid Leukemia) the audio-tape was offered to the family and was followed (2-3 months later) by a structured, anonymous questionnaire sent by mail.
Results: 63/63 families accepted the tape recording; 3/63 did not withdraw the cassette. In 49/60 (81.6%) we received back the filled questionnaire. 43/49 (87.7%) appreciated to receive the cassette and 40/49 (81.6%) have listened it again at home (mean 2.9 times). 82.9% acknowledge that re-listening the cassette help them in better understanding different aspects of the communication and 60.9% said that they better remembered what they heard at diagnosis. 39/49 (79.5%) considered very useful this procedure suggesting us to continue; only 11 families (22.4%) communicated us that listening the cassette generated anxiety.
Comments: The usefulness of the audio-taping is still to be demonstrated. In our setting the parents appreciated this approach confirming the usefulness in better understanding the different aspects of the communication and suggesting us to continue. Any psycho-social intervention should be critically evaluated. The point of view of parents could be an active contribution that allows a better adjustment of the different interventions to the true needs of the involved people.

O-198

ENHANCED QUALITY OF LIFE IN LONG-TERM SURVIVORS OF CHILDHOOD LEUKEMIA AND THEIR FAMILIES: A SIX-YEAR LONGITUDINAL FOLLOW-UP STUDY

J.J.Spinetta*, L.Adamoli, D.Fraschini, A.Corbetta, M.Jankovic and G.Masera
*Psychological Dept. University S.Diego - USA and Dept. of Pediatrics, University of Milan - Italy

Objective: Adjustment of cured child and family; A six-year prospective study of 58 families. Results: Increase in survivors' coping skills: early intervention effective.

A central area of study and concern in psychosocial childhood leukemia research is what happens to long-term survivors and their family members. Does the cured patient-now a young adult-fare as well in life as before, or even better? What happens to the other family members, to the mother and the father and the siblings who have shared in the stress-filled life event?

This six-year longitudinal study of 58 families of children undergoing treatment for leukemia at the pediatric hematology service at San Gerardo Hospital, Monza (University of Milan School of Medicine) found (1) that long-term survivors had significant increases in areas of personal strength and coping after going off therapy, (2) that families who scored at the lowest level of functioning at diagnosis (bottom 25%) as a group retained that low level 4 years after going off therapy, but (3) that a program of early intervention for families at high risk for psychosocial problems at point of diagnosis was effective in giving many of the families an increase in coping skills. Two instruments are discussed: The Family Adjustment Scale (FAS) (Spinetta,1981) and the Current Adjustment Scale (CAS) (Spinetta, 1989).

O-93

A SCHOOL AND SOCIAL REINTEGRATION PROGRAM FOR CHILDREN AND ADOLESCENTS WITH CANCER.

Marie-Louise C.G. Biemans, Bob F. Last, Willem A. Kamps.
Academic Medical Center, University of Amsterdam,
Emma Kinderziekenhuis AMC, Paediatric Psychosocial Department,
P.O. Box 22700, 1100 DE Amsterdam, The Netherlands.

Objective: With this study we expect to obtain more knowledge on social adaptation and psychological functioning of children and adolescents with cancer. The aim of the study is to improve social functioning and competence, and emotional well-being, and return to school of children aged 8 - 16, with newly diagnosed cancer. We expect to achieve these goals by conducting a standardized intervention program early in the course of the illness.
Research questions:
1. Does the intervention program improve social functioning, social competence and emotional well-being of children and adolescents with newly diagnosed cancer?
2. Does the intervention program facilitate school-reentry?
Methods: Data were collected in the control group first and subsequently in the intervention group. In both groups data were acquired on psychological and social adjustment and school functioning at three measurement points; at the start of the treatment, three months later and nine months after the first assessment. Information was obtained from 65 patients, parents, class teachers and primary physicians. Intervention consisted of stimulating patients and parents in their return to pre-illness activities. Therefore children in the intervention group were invited to participate in a video-training. The emphasis in the training was on: contact with peers during treatment, and schoolwork, and communication about the disease with peers. Furthermore children were

encouraged to prepare a classroom presentation about their illness and treatment.
Results: Findings in the control group suggest that children with cancer experience more behavioral problems and experience themselves as less social competent. This is also reported by parents and teachers.
Conclusions: Absence from school is not always a result of the state of physical health or effects of treatment. An intervention program early in the course of the illness may result in less school-absence and may improve psychological and social functioning of children and adolescents with cancer.

O-94

EFFECTIVE TRAINING OF ATTENTION AND MEMORY IN CHILDREN WITH CANCER

C.M.C.M. Hendriks and B.F. Last
Emma Kinderziekenhuis Academic Medical Center, Pediatric Psychosocial Department, Amsterdam, the Netherlands

Cognitive disturbances and subsequent school problems in children with cancer have been reported for two decennia. The call for intervention increases. The present study evaluates whether intervention directed at improvement of attention and memory functioning is effective.
The effectiveness of 'the Amsterdam Memory and Attention Training for children (AMAT-c)[1)] was investigated in 44 children with cancer. Two groups of children, trained (n=25) and controls (n=19), were compared. Neuropsychologic functioning in all children was assessed three times with a half year interval; at pretest, posttest and at follow-up. In addition parents and teachers of all children received a schoolfunctioning questionnaire at the same times. The AMAT-c was applied in the trained group between pretest and posttest. Controls received training after follow-up. All children aged 8-18 years completed cancer treatment and were diagnosed with significant attention and memory disturbances.
Children in both groups did not differ on age, degree of neuropsychological disturbance, sex, age at diagnosis, interval between diagnosis and pretest, diagnosis for cancer. The results showed that children in the trained group did significantly better than controls at posttest. This positive effect of the training was found to be continued at follow-up, after training was stopped for half a year. The performances of the trained children increased on mental tracking, short term memory and daily memory functioning.
After one year the results of the schoolfunctioning questionnaire revealed a significant decrease of learning difficulties in children who were trained but not for the children in the control group.
The results indicate that the AMAT-c is an effective instrument for improvement of attention and memory functions in children with cancer. Moreover this intervention may result in a decrease of their learning difficulties.

1) Hendriks, C.M.C.M., & van den Broek, T.M. (1996) Amsterdamse Training van Aandacht en Geheugen voor kinderen. Handleiding en Werkboek. Swets & Zeitlinger, Lisse, The Netherlands.

O-197

Promoting Health Protective Behaviors in Childhood Cancer Survivors.

MM Hudson, V Tyc, J Gattuso, A Quargnenti, D Crom, C Mason, DK Srivastava, P Hinds. St. Jude Children's Research Hospital and the University of Tennessee, Memphis, College of Medicine.

We initiated a randomized controlled pilot study termed "Protect" in July 1995 in our After Completion of Therapy Clinic to determine if educational interventions could increase childhood cancer survivors' knowledge of cancer and risks for late effects, and promote the adoption of health protective behaviors. Patients were randomized to an Intervention Group (IG) or a Standard Care (SC) Group. In the IG, health practices were targeted individually, based on treatment, family, and social history, and focused on specific behaviors that influence cancer risk. Components of the intervention included 1) personalized cancer and late effects risk counseling accompanied by a written treatment summary, 2) health goal commitment and training in health protective behavior, and 3) telephone follow-up. The intervention was administered by a team of research nurses, nurse practitioners, and pediatric oncologists and incorporated into the survivor's annual evaluation. Thus far, 254 adolescent survivors, aged 12-18 years, have been enrolled on the study; 142 were female and 218 were white. Health goal commitments selected by participants (n=120) randomized to the IG included reducing dietary fat (n=33), losing weight (n=24), performing regular aerobic exercise (n=26), using sun protection (n=13), performing monthly breast (n=8) or testicular (n=8) self examination, and stopping tobacco use (n=7). Differences between the IG and SCG in knowledge and understanding of late effects will be assessed by two-sample t-tests. Assessment of the intervention's efficacy in changing health behaviors in the IG will be assessed by examining the frequency of survivors adopting the health behavior. Preliminary experience with this pilot supports the feasibility of educational intervention research in a specialty clinic dedicated to monitoring long-term survivors. We plan to accrue a total of 275 pts, and will report 6 and 12 month follow-up data for knowledge variables and practice of health behavior.

O-95

THE ROLE OF THE ONCOLOGY RESEARCH NURSE

D Easlea, Department of Oncology, Birmingham Children's Hospital NHS Trust, Birmingham, B16 8ET.

There is no single definition of the role of the Research Nurse as posts seem to be shaped according to employers needs. Some post holders concentrate on nursing issues while others are primarily employed to work on Clinical Trial programmes. The role was originally developed in America in the early 1970's and the first research nurses worked to develop better drug administration techniques and to improve patient care. In time they became recognised as valuable members of the research team. I have been in post at the Birmingham Children's Hospital NHS Trust since January 1994. The post was developed in order to facilitate the development of Phase I and II clinical trial programmes within the oncology department to ensure a high standard of practice and patient care. The core responsibilities of my role are outlined briefly below :

* Sharing expertise in the development of medical/nursing clinical trials in oncology.
* Informing patients about the experimental nature of treatment.
* Developing and introducing nursing treatment protocols.
* Planning and co ordinating the research requirements with daily patient care in collaboration with nursing/medical colleagues.
* Co ordinating the conduct of clinical trials and identifying potential problems.
* Collecting, organising and recording the data collected in the trials such as toxicity assessment.
* Educating colleagues and keeping them up to date on all the latest information in oncology via teaching, networking and publishing.
* Reporting physical and psychosocial responses to treatments, locally, nationally and internationally.

O-96

THE EFFECTIVENESS OF A PAEDIATRIC ONCOLOGY LINK GROUP

Mills A, Phillips M, Menon J, Phillips,C

Llandough Hopital in Cardiff is the only United Kingdom Childhood Cancer Study Group (UKCCSG) centre in Wales. Referrals to the centre

are from a wide geographical area. Between 60 and 70 children are referred to the centre annually.

It is accepted that regionalisation of management of the child with cancer optimises the care and survival rates for these children. However, prior to confirmation of the diagnosis of cancer or where practical local care is planned generic paediatric nursing colleagues feel deskilled in the care of the child with cancer. Their lack of knowledge is frequently observed by parents. In response to these negative perceptions a "Paediatric Oncology Link Group" was formed at this centre.

The group meets 3 times per year to share information and provides an update of basic theoretical paediatric haematology/oncology and practical skills. Preliminary assessment by the nurses from within the group has identified an improvement in attitude, knowledge and skills. This is currently being objectively confirmed. The profile of the group, the development of the study days and the results of questionnaires assessing the impact of the group will be presented.

O-97

Title: THE SYSTEM OF PRIMARY NURSING

Name(s) of author(s),institution,city,country:
Boek.M and Kuiper.R, both RSCN
EmmaKinderZiekenhuis/AMC Department of Paediatric Oncology
Amsterdam, The Netherlands

Abstract:

Primary Nursing:

At the Paediatric-Oncology ward in the EKZ/AMC in Amsterdam children from 1 to 18 years old with cancer are being treated.
There are about 120 new patients each year.

In the AMC we work according to the system of integrated nursing. Primary nursing was introduced at our ward in November 1995. This means that every new patient during his first admission is assigned to one primary nurse (PN). He/she will be the PN during the whole treatment, which can last up to 1 or 2 years.
During the hospital admissions, this PN controls the nursing process. This doesn't mean that the PN will always nurse the child by him/herself.

The PN keeps the nursing file, makes a nursing plan and organizes conferences about the child, if requested. He/she also maintains relations with all members of the multi-disciplinary team both in- and outside the hospital.

At the end of the treatment the PN has a final talk with the parents and the child to evaluate the care which has been presented. If a child can not recover and goes home to die, the PN keeps contact with the parents by telephone. After the child's death there is an opportunity for the parents to have a post mortem conference with the PN where they can also evaluate the nursing.

The great asset of this way of nursing is that parents and child always have a regular nurse where they can come to with all their questions and speak about their problems.

Primary nursing benefits continuity and therefore quality of nursing.

O-98

Challenge, Change, and Creation in Cancer Care: Communication for Transformation.

Maddie Hooton. Practitioner lecturer.
Tracey Forrester. Macmillan Clinical Co-ordinator.
Child / Adolescent Oncology. Newcastle upon Tyne, England.

Aim.
To share our process of collaborative reflective practice, within critical incident technique, as a learning tool and vehicle for change, including current success and future projections.

Abstract.
"Pediatric oncology nurses are exposed to a variety of work related stressors in their clinical settings" and " because stress can contribute to burnout in oncology nursing, impair job performance and hinder nurse retention, the identification of specific stressors is the first step in determining unique interventions to reduce nurse stress responses".(1)
The future is certain; caring for children with cancer, and their families will remain an endeavour which stretches the personal and professional resources of all professionals involved in this process. However, we are aware of the lack of appropriate opportunities where nurses can "reflect on their experience, make it more explicit through having to share it, interpret it and recognise it as a basis for future learning; and escape from their experience in the sense of challenging assumptions and acquiring new perspectives" (2).
We believe we have set up a successful framework, through the use of critical incident technique, to enable shared communication, debate and analysis of any issues or problems in our past, present or future, to enable collaborative and proactive change which both supports professionals accountability and autonomy and protects families by providing the best standards possible within current health care contexts.

1. Carlson Bond, D. (1994)
The Measured Intensity of Work Related Stressors in Pediatric Oncology Nursing.
Journal of Pediatric Oncology Nursing. Vol. 11. No. 2.
2. Eraut, M. (1985)
Knowledge Creation and Knowledge use in Professional Contexts.
Studies in Higher Education Vol. 10 No.2

O-99

EPSTEIN-BARR VIRUS IN PAEDIATRIC HODGKIN'S DISEASE PATIENTS IN RUSSIA.

E.E. LEENMAN, P.F. AMBROS, AND K.M. POZHARISSKI
Department of Pathology, Petrov Institute of Oncology, St.-Petersburg, Russia (E.E.L, K.M.P); CCRI, St. Anna Kinderspital, Vienna, Austria (P.F.A).

Aim: The association of Epstein-Barr virus (EBV) and Hodgkin's disease (HD) has been suggested by serological, epidemiological, and molecular biologic studies and shows variation between different geographic areas. In the present study, we investigated the frequency of latent membrane protein-1 (LMP1) positivity in Russian HD cases.
Methods: We evaluated 17 cases of HD in children and adolescents which were diagnosed in our institution during 1994-1995. The age of patients ranged from 6 to 21 years (5 < 15y, 12 >15y), while male to female ratio was 0,42. Lymph node biopsies were examined for presence of EBV infection by immunostaining with anti LMP-1 antibodies. A given biopsy was considered positive if distinct specific cytoplasmic, membrane or Golgi-zone staining was seen in the pathognomonic Hodgkin and Reed-Sternberg cells (H-RS). Additionally, all cases were investigated with a panel of antibodies, including Ber-H2 (CD30) and M-1 (CD15).
Results: LMP-1 positive H-RS cells were found in 3/3 cases of HD with mixed cellularity subtype, whereas only 8/14 of nodular sclerosis cases showed specific staining, giving a total number of 65% positive cases in the studied group (11/17). In patients under 15 years of age 80% of lymph nodes showed LMP-1 positivity in H-RS cells, whereas patients between 16 and 21 years of age displayed positive reaction in only 60% of analysed lymph nodes. In female patients, we observed a higher rate (75%) of EBV infection than in male patients (40%).
Conclusion: The results of the study indicate that EBV is consistently associated with paediatric HD cases in Russia and was detected in approximately two-thirds of the patients. EBV was found to be more frequent in patients with mixed cellularity histologic subtype, age below 15 years and female sex.

O-100

SURVIVAL OF CHILDREN WITH NON-AFRICAN BURKITT'S LYMPHOMA DIAGNOSED OVER A 50 YEAR PERIOD

J.Y.Tang, S.Kahwash, A.Rauck, C.Hutchison, W.A.Newton, F.B.Ruymann. Children's Hospital at the Ohio State University, Columbus Ohio

180 patients with non-Hodgkin's lymphoma have been treated at our hospital since 1945. Their tumors have been reviewed and re-classified mainly according to the Working Formulation utilizing current immuno-histochemistry as necessary since tissue blocks were available in most cases. This report will summarize the clinical data of sixty-five that were classified as Burkitt's lymphoma.

The incidence/year, after 1969, was relatively constant with an average of 2/year (S.D.±1.5). The M:F ratio was 3:1. Their ages at diagnosis ranged from two to sixteen years with suggestive peaks at 5 and 10. Blacks were under-represented. Sites were predominately in the GI tract (52.4%), head and neck (38.3%) with only one suggestive of African type, located in the parotid area. Extent of disease was local in 12.3%, regional in 41.5% and distant-38.5%

Chemotherapy was not intensive until CCG's COMP-LSA2L2 study was begun in 1976. Five-year survival for patients diagnosed in the period 1945-1970 (11 patients) was 36.4%, 38.5% in the 70's (13 patients) , 53.8% in the 80's (26 patients), and 86.6% thus far in the 90's (15 patients). **Conclusion:** 5 yr. survival of patients with Non-African Burkitt's tumor was surprisingly better than expected before intensive multiagent chemotherapy was introduced. A significant improvement in survival at our institution, however, did not occur until the 90's when more specific, intensive regimens for non-lymphoblastic NHL were introduced.

O-101

DETECTION OF NUCLEOPHOSMIN-ANAPLASTIC LYMPHOMA KINASE (NPM-ALK) IN PEDIATRIC LARGE CELL LYMPHOMA USING MONOCLONAL ANTIBODY ALK 1

AH Uner, MP Link, J Laver, M Schwenn, SW Morris, K Pulford, DY Mason, D Barrett, and RE Hutchison. SUNY-HSC, Syracuse NY, John Radcliffe Hospital, Oxford UK, St. Jude Children's Research Hospital, Memphis TN and the Pediatric Oncology Group, Chicago IL

Objective: The purpose of this study was first, to determine the presence of nucleophosmin-anaplastic lymphoma kinase (NPM-ALK), associated with t(2;5)(p23;q35) in anaplastic large cell lymphoma (ALCL), in children undergoing treatment for large cell lymphoma on Pediatric Oncology Group protocols. Second, to assess its correspondence with CD30 and ALCL morphology.

Methods: Paraffin-embedded formalin or B5-fixed tissue was available from 19 patients with large cell lymphoma treated on POG protocols #9219 (localized) or #9315 (advanced stage). Immunophenotyping was performed by a streptavidin-biotin-peroxidase method using antibody ALK1 as well as B-cell marker CD20, T-cell markers CD3, CD45Ro, and CD43, and Hodgkin/ALCL marker CD30. Histologic classification was by the Working Formulation (WF) and the Revised European American Lymphoma (REAL) classification.

Summary: Thirteen cases could be classified as ALCL. Of these, 11 were T-cell and 2 non-T, non-B. 13/13 ALCL labelled with both anti-CD30 and ALK1. Six cases were diagnosed as large B-cell lymphoma and of these 0/6 were reactive with anti-CD30 or ALK1.

Conclusions: Our patient population includes large B-cell lymphoma and, more frequently, ALCL. The majority of our pediatric ALCL are reactive with ALK1, consistent with NPM-ALK expression. It is likely that a majority of pediatric ALCL thus constitute a distinct entity. The prognostic significance of this entity may be better defined when data is available on a larger number of patients.

O-102

PATIENT CHARACTERISTICS OF 4 CHILDREN WITH ANAPLASTIC LARGE CELL LYMPHOMA (ALCL) ASSOCIATED WITH A TRANSLOCATION T(2;5) (P23;Q35) AND ANAPLASTIC LYMPHOMA KINASE (ALK) EXPRESSION

P Brock[1], E Van Damme[1], M Depraetere[1], S Pittaluga[2], C De Wolf-Peeters[2], I Wlodarska[3], H Van Den Berghe[3], L Breysem[4], A Uyttebroeck[1]. Catholic University of Leuven, Department of Paediatrics[1], Pathology [2], Cytogenetics [3] and Radiology [4], Leuven, Belgium.

Since 1993, at our institution we have tried to clarify the clinical entity diagnosed as ALCL or ALCL related disease. This diagnosis was made on morphology in 7 children. 4 cases were considered to be ALCL and 3 to be Hodgkin's-like ALCL (HD-like ALCL). All 4 ALCL cases showed cytoplasmic immunostaining with ALK1 antibody which recognised the native ALK protein as well as the fusion product of the t(2;5). The translocation was found by cytogenetics in two cases, and was confirmed by FISH assay in two other ALCLs. In contrast, all three HD-like ALCLs were negative for ALK1 immunostaining and t(2;5), although they were characterised by complex chromosomal abnormalities. We present the patient characteristics of the 4 ALCLs.

N°	Age yrs	Stage Murphy	Adenopathy	Bone	Phenotype	Chemo-therapy	ABSCT
1	12.6	II	axillar	-	null	901 °	-
2	12.7	II	inguinal	unifocal	T	901 °	-
3	8.5	III	mediastinal	multifocal	T	902 °	+
4	9.0	III	mediastinal	multifocal	null	902 °	+

° UKCCSG

Patient 2 had an initial spontaneous remission of an isolated bone lesion of the acetabulum, she then relapsed locally and was treated. Patient 3 relapsed in the skin 2 weeks after chemotherapy, PET scan and biopsy were positive. Patient 4 had a persistent mediastinal mass after chemotherapy, which was positive on PET scan, and therefore received 21 Gy involved field radiotherapy. Both patient 3 and 4 were conditioned with BEAM chemotherapy and given a peripheral blood stem cell (PBSC) transplant. All are currently well and disease free, now 3 yrs, 1.5 yrs, 8 mos and 9 mos off treatment. In future collaborative studies of ALCL we suggest using ALK expression, by immunohistochemistry, as a simple method of identifying ALCL patients with the same biological disease for purposes of comparison.

O-103

BONE HISTOMORPHOMETRY IN CHILDREN WITH NEWLY DIAGNOSED ACUTE LYMPHOBLASTIC LEUKEMIA

Leeuw JA[1], Koudstaal J[2], Wierserna-Buist J[2], Timens W[2], Kamps WA[1]. [1]Children's Cancer Center and [2]Dept. of Pathology, University of Groningen, The Netherlands.

Objective: To elucidate the balance between bone formation and re-sorption in children with newly diagnosed acute lymphoblastic leukemia (ALL).

Methods: In 24 consecutive children with ALL a bone biopsy was taken from the crista iliaca posterior by a vertical approach with a 2 mm core trephine. Biopsies were taken under ketamine anaesthesia together with the diagnostic marrow aspiration, before any treatment was given. Biopsy samples were fixed in 2% paraformaldehyde and embedded in a glycol methacrylate medium. In five sections (2µm) with an interspace of 100µm the following parameters of cancellous bone were assessed: bone volume, bone area, trabecular thickness, osteoid volume, osteoid area (active and inactive), osteoid width, number of osteoblasts, erosion area (active and inactive) and

number of osteoclasts. Data were compared with biopsies from 16 children, obtained during the work-up for other malignancies (only patients without bone marrow involvement were included); and with histomorphometric data of normal children from the literature.

Results: In ALL patients bone volume and trabecular width were normal to decreased. No patient showed increased active bone resorption. Active osteoid formation was decreased in most patients, but with a wide range. Children under 10 years had more serious pathology, while adolescents had decreased osteoid formation, but rarely decreased bone volume. No clear correlation with duration of complaints, immuno-phenotype or tumor burden could be found. Children with cancer other than ALL and localized disease had histomorphometric data in the normal range, while patients with advanced disease showed a pattern like ALL patients, but to a less extent.

Conclusions: ALL results in osteblastic dysfunctioning and a reduced bone volume, but bone resorption is normal or even slightly suppressed. Patients with other malignancies and advanced disease show the same bone anomaly, suggesting a common causal mechanism in ALL and other childhood cancers.

O-104

ANAPLASTIC WILMS' TUMOURS - THE SIOP 9 TRIAL AND STUDY EXPERIENCE WITH THE NEW DEFINITIONS

Vujanic GM, Weirich A, Sandstedt B, de Kraker J, Delemarre JFM, Harms D - for the SIOP Nephroblastoma Committee

Anaplastic Wilms' tumours (AWTs) have been originally subclassified as focal (FA) and diffuse anaplasia (DA) but there was no difference in survival between the two groups[1]. However, the new definitions of FA and DA have shown for the first time a difference in survival[2].

The aim of our study was to establish whether the new definitions could be applied to AWTs in the SIOP 9 trial and study.

There were 1123 patients with unilateral WT under 16 years of age registered and reviewed by the Panel.

Fifty three AWTs (4.7% of all cases) were found including 34 (64%) with FA and 19 (36%) with DA (old definitions). The age distribution was as follows: 1st year - 1 (2%) pt; 2nd - 2 (4%); 3rd - 5 (9.5%); 4th - 5 (9.5%); 5th - 12 (23%); and >5 yrs - 28 (53%) pts. There were 12 (23%) stage I; 13 (24%) stage II, 11 (21%) stage III, and 17 (32%) stage IV pts. The overall survival was 47% (25/53 pts) and it was remarkably same for both FA (16/34 pts - 47%) and DA (9/19 pts - 47%).

When reclassified according to the new definitions, 25 cases of FA were moved in the DA group. The age and stage distribution for FA and DA showed no difference, but the survival was strikingly different: 67% (6/9 pts) for FA and only 43% (19/44 pts) for DA.

41/53 pts (77%) received pre-operative chemotherapy resulting in marked chemotherapy-induced changes but features of anaplasia were still easy to recognise. Thus, the new definitions of FA and DA are applicable to pre-treated WTs and proving to be a new prognostic parameter.

[1] *Cancer 1978; 41: 1937-48*
[2] *Am J Surg Pathol 1996; 20:909-20*

O-105

IS ABSENCE OF PERITUMORAL GLIOSIS A FAVORABLE PROGNOSTIC FACTOR IN MEDULLOBLASTOMA (MB) ?

D. Frappaz*, A. Jouvet**, N. Dufay***, C. Mottolese**, P. Bret**, S. Soulié*, MF. Belin***, N. Thomasset***
* Centre Léon Bérard, ** Hôpital Wertheimer, *** INSERM U 433

Tumor from peripheral nervous system (PNET) have been characterized according to biological factors including Shimada histological classification, N-myc amplification, CD44 or NGFr expression, ploidy.They are reliable tools for prognostic and allow a tailoring of therapy according to these factors. Conversely, for PNET from CNS and especially MB efforts to identify tumoral markers such as DNA ploidy, mitotic index, oncogen amplification, differentiation markers, suppressor gene expression are still controversial as useful prognostic tools. We report here the absence of gliosis expression in the peritumoral stroma as a new prognostic factor in MB.

Material and Methods : We retrospectively reviewed 48 cases of MB treated in Centre Léon Bérard from 11/85 to 10/96. Twenty four patients were selected because of the following criteria : 1) homogeneous treatment by surgery, chemotherapy followed by craniospinal radiation 2) availability of tumoral and peritumoral tissue. The tumor was studied histologically and with immunostaining for differentiation (glial and/or neuronal). Gliosis in the peritumoral stroma was characterized histologically and by immunochemistry for GFAP and quoted as positive or negative.

Results : We showed that the absence of gliosis in the peritumoral stroma linked to a favorable outcome in MB. It was the only significant prognostic factor : in the absence of gliosis in peritumoral tissue (7 pts), DFS was 100% versus 47% in 17 patients with gliosis at 10 years (p = 0.04).

Comments : If the absence of gliosis is confirmed by larger studies as a marker of good prognosis, this may allow a decrease in therapy and sequelae in a subgroup of children with very good prognosis. The underlying mechanism of peritumoral gliosis remains speculative : paracrine secretion of inductive factors for gliosis by tumoral cells ?

O-106

PROGNOSTIC FACTORS IN CHILDHOOD PERIPHERAL PRIMITIVE NEUROECTODERMAL TUMORS (pPNETSs) OF BONE.

R.Luksch, G.Sampietro, P.Collini, R.Giardini, M.Massimino, G.Cefalo, M.Casanova, L.Gandola, L.Migliorini*, F.Fossati-Bellani, L.Scopsi. Istituto Nazionale Tumori, Milano, and *Ospedale Fornaroli, Magenta MI; Italy.

Objectives: to evaluate the prognostic impact of some clinico-pathological features in a series of children with osseous pPNETs. ***Patients and Methods:*** the analysis was carried out on a series of 73 consecutive pts with tumor tissue available for the study purposes over a 18-year period. There were 48 M and 25 F (median age 12 yrs; median follow-up 38 months, range 1-231). At the time of this analysis, 19/73 patients were alive NED, one had ED, 53 had died (50 of progressive disease, 3 of other causes). The univariate analysis of overall survival (OS) according to Cox regression model considered the following variables: sex, age, serum LDH, primary tumor site, infiltration of adjacent soft tissues, loco-regional nodes, distant metastases, treatment applied, macroscopic residual disease after treatment, tumor mitoses, rosettes and/or pseudo-rosettes and/or neuropilum (morphological neural markers, MNM). For the multivariate analysis of OS the variables with unadjusted hazard ratio (UHR) significantly different from 1 were considered (63 evaluable patients). ***Results:*** prognostic significance in univariate analysis is shown by the following table:

VARIABLES	*UHR*	*95% C.I.*	X^2	*P*
DISTANT METASTASES				
absent vs present	2.52	1.33-4.79	8.049	0.0046
RESIDUAL DISEASE				
absent vs present	4.94	2.73-8.96	27.78	0.0001
SERUM LDH				
normal vs pathological	2.37	1.30-4.31	7.998	0.0047
MITOSES				
absent vs present	2.24	1.19-4.21	6.237	0.0125
MNM				
absent vs present	1.93	1.08-3.44	4.931	0.0264

In the final model of the multivariate analysis only two variables - residual disease after treatment (adjusted hazard ratio, AHR= 4.68; p = 0.0001), and serum LDH (AHR= 2.20; p = 0.01) - were retained. ***Conclusions:*** In the present series, serum LDH pathologic value at diagnosis and the presence of macroscopic residual disease after the end of the treatment were the most significantly adverse prognostic factors.

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O-107

NEURAL DIFFERENTIATION AND PROGNOSIS IN EWING TUMORS: THE (EI)CESS EXPERIENCE

H. Schubert[1], S.Ahrens[1], Ch.Hoffmann, M.Paulussen[1], B.Dockhorn-Dworniczak, H.Jürgens[1], D. Harms
[1]Dept. of Pediatric Hematology/Oncology University of Münster, Germany

Background: The prognostic impact of varying degrees of neural differentiation in Ewing-tumors has been the subject of controversy. In histopathological diagnostics, the immunohistochemical markers most commonly used for the detection of neural features in Ewing tumors are neuron-specific enolase (NSE) and protein S100.

Material and Methods: In order to assess the prognostic significance of either or both of these markers, we analyzed outcome according to neural marker expression in primary tumors of 198 patients with Ewing tumors treated in the consecutive (EI)CESS studies. All patients were reviewed for pattern of NSE and protein S100 expression. The original histopathologic diagnoses were "typical" Ewing's sarcoma in 95 cases, "atypical" Ewing's sarcoma in 34, and "malignant peripheral neuroectodermal tumor (PNET/MPNT)" in 68 cases, respectively. Survival times were estimated by the method of Kaplan and Meier for all patients, comparisons made by logrank test.

Results: Positive staining for NSE was reported in 100 of 198 cases, 55 cases showed expression of protein S100. Positive staining for other neural markers was reported only occasionally: synaptophysin (4/30), glial fibrillary acidic protein (1/18), chromogranin (1/56), neurofilament protein (1/33), Leu7 (3/35). Statistical analyses showed no significant correlation between patients' relapse-free survival and presence or absence of any single, or any combination of neural markers.

Conclusion: Once the diagnosis of a Ewing tumor is established using morphological features, p30/32-MIC2-antigen, and eventually molecular-genetics, the differential expression of neural markers such as NSE or S100 has no impact on prognosis in patients treated according to the (EI)CESS protocols.

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O-108

Melanotic Neuroectodermal Tumor of Infancy a case report

Drs PIM Worm[1], Drs J Groot-Loonen[1], Drs CA van de Kaa[2], Dr PCM de Wilde[2], Dr H Caron[3], Drs E Meier[3]. Department of Pediatric Oncology[1] and Pathology[2], University Hospital Nijmegen, Department of Anthropogenetics[3], University of Amsterdam, The Netherlands.

Introduction: Melanotic neuroectodermal tumor of infancy (MNTI) is a rare neoplasm that most often occurs in infants under 1 year of age.
MNTI is a primitive neuroectodermal tumor with polyphenotypic expression of neural and epithelial markers, melanin production, occasional glial and rhabdomyoblastic differentiation. It presents as a pigmented, fast growing expansion, usually located in the maxilla. Because the tumor is considered to be benign, conservative excision is the treatment of choice; the rate of local recurrence after excision is 15%. The malignancy rate is approximately 2%.
Case: A 5 month-old male infant was referred because of an enlarged right posterior mandibullary alveolar ridge. Intraoral examination revealed a nonulcerated, blue-black pigmentated swelling centered over the right mandibullar alveolar process.
24 h urinary vanilmandelic acid (VMA) levels were within normal range.
Pathology: Microscopically there were two populations of cells i.e., small neuroblastic cells and larger melanin-containing epithelial cells supported by a fibrous stroma. There was a predominance of neuroblastic cells, which were positive for synaptosin and NSE.
There was a small amount of melanin-containing cells, mildly positive for vimentin.
Genetical investigations: PCR analysis with highly polymorphic CA-repeat markers was performed on tumour and constitutional DNA of the patient and his parents. Uptill now those analysis demonstrated Loss Of Heterozygosity (LOH) of chromosome 1p for the maternally derived homoloque. To further delineate the cell lineage of this MNTI the possible presence of N-myc amplification and/or a Ewing-family rearrangement are being investigated
Conclusion: First report of a chromosome 1p deletion in MNTI.

O-109

ASSESSMENT OF PROLIFERATION ACTIVITIES AND P-GLYCOPROTEIN IN PEDIATRIC MALIGNANT LIVER TUMOR WITH RECURRENCE

Y. OKAWA, M. FABRE, F. SASAKI*, Y. HATA*, F. GAUTHIER, J. VALAYER, C. H. U. Bicêtre, Le Kremlin-Bicêtre, FRANCE, *Hokkaido University, Sapporo, JAPAN

Drug resistance often appears after repeating chemotherapy and it remains a major therapeutic obstacle to improving the outcome for children with malignant liver tumor, nevertheless the usual chemosensitivity of this disease.

Purpose and methods: The aim is to determine the cell proliferation and the expression of P-glycoprotein(P-gp) in pediatric liver tumor tissue from patients with or without recurrence after operation. From 1986. 12 to 1995. 11, 18 children aged 1. 2 to 14 years have been operated on after chemotherapy. Five children had local recurrence 1 or 2 times. With PC-10 and C494 which recognized P-glycoprotein, 26 tissue specimens of primary and recurrent tumors were stained using an avidin-biotin immunohistochemical technique. Immunoreactivity was scored by labeling index(LI) in PCNA and by estimating the area of positive tumor cells in P-gp.

Results: The average PCNA LI of each group is as follows; primary tumor without recurrence(NR): 55. 2%(31. 3-75. 7), tumor with recurrence(1R): 56. 6%(41. 6-79), the first recurrent tumor(2R): 71%(59. 4-79. 2). It shows the tendency of increase of PCNA LI after recurrence, but there was not significant difference between each group. NR showed immuostaining of P-gp over 50% in 3 of 12 cases(25%), while 5 of 5(100%) in 1R tumors.

Conclusions: Our data show that an increase of PCNA LI in the recurrent tumor cells after chemotherapy. The observation of high percentage of P-gp expression in recurrent group suggests the existance of viable tumor cells that resist to multidrug from the first operation.

O-110

IMMUNOHISTOCHEMICAL ANALYSIS OF PROLIFERATION MARKER MIB-1 EXPRESSION IN PEDIATRIC MALIGNANCIES

Takaharu Oue, Masahiro Fukuzawa, Takeshi Kusafuka, Yosuke Kohmoto, Tasnim Ara and Akira Okada, Department of Pediatric Surgery, Osaka University Medical School, Osaka, Japan.

Object: Proliferative markers are related to tumor behavior. The monoclonal antibody MIB-1 reacts with the same epitope recognized by Ki-67 which appears in the nucleus of the proliferating cells and can be detected immunohistochemically in paraffin embedded tissues.
The aim of this study is to analyze MIB-1 expression in various primary pediatric malignancies and to evaluate the usefulness in the assessment of the proliferative activity and prognosis.
Materials and Methods: Ninety nine pediatric malignant tumor resected at Osaka University Hospital (Neuroblastoma:45, Wilms

tumor:23, Hepatoblastoma:7, Rhabdomyosarcoma:13, other soft tissue sarcoma: 11) were available for examination. Formalin-fixed paraffin sections were immuno-stained with a monoclonal antibody MIB-1 using the streptavidin-biotin immunoperoxidase method. Ten fields were chosen at random and at least 1,000 tumor cells were counted. The labeling index(LI) was calculated as the percentage of positive cells.
Results: (1)MIB-1 expression was confined to the nucleus of proliferating cells. Mean LI was 22% in neuroblastoma, 46% in Wilms' tumor, 31% in hepatoblastoma, 44% in rhabdomyosarcoma and 31% in soft tissue sarcoma (2)In neuroblastoma, LI was significantly higher in advanced cases, undiferentiated tumors and unfavorable histology of Shimada's calcification. (3)In hepatoblastoma, LI was significantly higher in advanced cases. (4)In rhabdomyosarcoma, LI was significantly higher in alveolar type than in embryonal type. (5)In soft tissue sarcoma, the patients with a higher LI(over 50%) have a significantly worse prognosis.
Conclusion: It is concluded that the immunohistochemical analysis of MIB-1 expression is useful to assess the proliferative activity of the pediatric malignancies and provide prognostic useful informations.

O-111

NOVEL MODULATORS (VX710 & PSC833) OF MULTIDRUG RESISTANCE (MDR) IN NEUROBLASTOMA CELL LINES.

Yanagisawa TY, Newman A, Pinkerton CR & Pritchard-Jones K. Section of Paediatrics, Institute of Cancer Research/Royal Marsden Hospital NHS Trust Hospital, Sutton, Surrey, UK.

Both MDR1 and MRP have been suggested as important determinants of treatment failure in neuroblastoma.
Aims: to examine the involvement of these MDR genes in drug resistance in neuroblastoma cell lines and evaluate the resistance reversal effects of MDR modulators.
Methods: Chemosensitivity was measured by both the MTS and clonogenic assays in 6 neuroblastoma and 3 control cell lines. Two novel modulators, PSC833 and VX710, were compared to cyclosporin A for their ability to reverse resistance to vincristine, doxorubicin, etoposide, taxotere, topotecan, cisplatin and melphalan. MDR status of the cell lines was examined by immunohistochemistry and RT-PCR for MDR1 & MRP expression.
Results: MRP was expressed in all and MDR1 in 4/6 neuroblastoma cell lines. All 3 modulators were able to reverse resistance due to either MDR1 or MRP in control lines; modulation was greatest (up to 100-fold) when due to MDR1 with vincristine as the substrate: lesser effects were seen on MRP (up to 4 fold). PSC833 and VX710 were as effective as cyclosporin A in modulating both MDR1 and MRP. However, VX710 could be used at higher concentrations which gave up to 2 fold better modulation in some cell lines. Drug resistance by modulators in neuroblastoma cell lines correlated better with MDR1 expression rather than MRP. Reversibility of resistance was in the order vincristine>> taxotere≥doxorubicin≥etoposide. No modulation of topotecan, cisplatin or melphalan sensitivity was seen.
Conclusions: Both PSC833 and VX710 show equal or greater activity than cyclosporin A in modulating drug resistance in neuroblastoma cell lines. The attraction of VX710 is its lack of toxicity in preliminary clinical studies where it can be safely used at concentrations of 5μM and may achieve better modulation. Both compounds merit further investigation in refractory/relapsed neuroblastoma. These *in vitro* data suggest that they should be best combined with vincristine, taxotere and/or an anthracycline.

O-112

INTRACELLULAR DAUNORUBICIN CONCENTRATIONS AND LRP ARE RELATED TO DRUG RESISTANCE IN CHILDHOOD LEUKEMIA

Veerman AJP[1], den Boer ML[1], Kazemier KM[1], Rottier MMA[1], Kaspers GJL[1], Scheper RJ[2], Janka G[3], Henze G[4], Creutzig U[5], and Pieters R[1].
Depts. of [1]Pediatric Oncology and[2] Pathology, University Hospital, Vrije Universiteit, Amsterdam, the Netherlands. [3]COALL Study Group, Hamburg, [4]ALL-REZ Group, Berlin, and [5]AML-BFM group, Münster, Germany.

Poor prognosis in both childhood acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML)is strongly correlated to in vitro drug resistance. To identify underlying mechanisms of resistance, we studied the intracellular accumulation of daunorubicin (DNR) by flow cytometry. In vitro drug resistance was determined with the MTT assay. The data were compared to the expression of P-glycoprotein (Pgp), multidrug resistance associated protein (MRP) and lung resistance protein (LRP), determined with monoclonal antibodies and flow cytometry.
Relapsed ALLs (R-ALL, n=27) were median 2.2-fold more resistant to DNR than 70 initial (I) ALLs ($p<0.001$). Cells of R-ALLs were larger than I-ALLs ($p<0.001$). When corrected for cell volume, the intracellular DNR concentration was median 1.4-fold lower in R-ALLs ($p<0.003$). The intracellular DNR concentration was correlated with in vitro DNR sensitivity (rho 0.45, $p<0.001$). Among 26 R-ALLs a higher percentage of cells stained LRP positive (using LRP56) as compared to 91 I-ALLs (51% vs 38%, $p<0.04$). Expression of LRP did not differ between early, late and multiple relapsed patients. The LRP expression was weakly correlated to DNR and etoposide cytotoxicity (rho 0.22 each, $p<0.04$).
AML samples (n=26) were median 1.9-fold more resistant to DNR than ALLs ($p<0.002$). The expression of LRP was median 1.7-fold higher than in 120 ALLs ($p<0.001$). Within the AML group, DNR cytotoxicity was not significantly related to LRP expression. Pgp (by C219 and MRK16) and MRP (by MRPr1 and MRPm6) expression were comparable (Pgp) or lower (MRP) in AML compared to ALL. Expression of Pgp and MRP did not correlate with DNR cytotoxicity in ALL and AML, nor with DNR accumulation in ALL.
In conclusion, LRP seems the most relevant resistance protein in childhood leukemias. Higher LRP, resulting in lower intracellular DNR concentrations, may explain DNR resistance in these leukemias.
Supported by the Dutch Cancer Society, grant VU93-641.

O-113

A THREE DAY DOXORUBICIN EXPOSURE OF HUMAN MES-SA CELLS SELECTS PREDOMINANTLY P-GLYCOPROTEIN EXPRESSING CLONES.

HCL Traunecker, MCG Stevens, DJ Kerr, DR Ferry.
CRC Institute for Cancer Studies, The Medical School, Birmingham and Department of Oncology, Birmingham Children's Hospital, United Kingdom

Resistant clones derived from a tumour cell line by continuous, multi-step selection with a cytotoxic agent have been used as *in vitro* model systems for the investigation of drug resistance mechanisms. These models have been flawed due to occurrence of multiple resistant mechanisms and induction of other biochemical epiphenomena. We selected clones resistant to doxorubicin (72hr exposure) by growing non-resistant tumour cell populations in parallel cultures over 15 generations, allowing for mutations to occur at random before exposure to the selecting agent (Luria-Delbrück fluctuation analysis).

Human uterine sarcoma cells, MES-SA, which do not express P-glycoprotein and failed to grow after exposure to 450 nM doxorubicin were expanded over 15 generations. Following a single 3 day exposure to 450 - 500 nM doxorubicin, clones were harvested over a 6 week period. The median mutation rate, calculated from 3 experiments, was 1×10^{7} mutations per generation. Overall 36 clones were isolated and analysed.

Ten clones were > 2-fold resistant to doxorubicin (MTT cytotoxicity assay). Eight resistant clones expressed P-glycoprotein as judged by Western blotting (monoclonal antibody JSB-1), RT-PCR and [^{3}H]-vinblastine binding. The biochemical basis of resistance in 2 clones remains to be defined. 2/26 clones, not resistant to doxorubicin on cytotoxicity testing, were positive for P-glycoprotein with all three methods and 2 further clones only with RT-PCR. The reason why non-resistant clones were selected could be due to inducable mechanisms of resistance or statistical survival of non-resistant clones.

Clearly, selection of P-glycoprotein expressing clones is the main reason for the failure of doxorubicin to kill all MES-SA cells after a short, single-step exposure. If these mechanisms are operative in human sarcomas, clinical strategies to eliminate these resistant clones, such as neoadjuvant modulation of P-glycoprotein by inhibitors should be further explored.

O-114

TREATMENT RESULTS IN 243 CHILDREN WITH HODGKIN'S DISEASE IN BULGARIA

Kalev I, Dr. Bobev, Tz. Russeva, I. Christosova, D. Konstantinov, Vl. Spassov, M. Sarbinova, G. Michailov, M. Iordanova, S. Marinova, Child. Oncol/Haemat. Clinic, Sofia, BULGARIA

From 1976 to 1996 243 (128 boys and 115 girls) children with M.Hodgkin were treated in our department. The median age was 9 years (9.3+-6.2). The clinical staging was: stage I-119 patients (48.97%), st. II-51 (20.99%), st.III-58 (23.86%), st.IV-15 (6.18%). The histological type of the disease was: lymphocyte predominance-33 cases (13.58%), nodular sclerosis-49 (20.16%), mixed cellularity-143 (58.85%), lymphocyte depletion-18 (7.41%). Patients were treated with protocols: MOPP-171 cases (70.37%), ABVD-15 (6.17%), MOPP+ABVD-37 (15.23%) and others - 27 patients (11.11%). Radio-therapy was included in 142 patients (58.44%). Positive EBV-serology was found in 48 of the cases (35.07%). Complete remission was achieved in all patients, alive are 134 (96.3%), 9 patients (3.70%) died. Seventeen relapses were diagnosed, confirmed by a second biopsy. Three of the children have had more than 3 relapses (1.23%). In 2 patients (0.82%) a second malignancy was registered (AML and astrocytoma).

O-115

CHILDHOOD HODGKINS DISEASE IN PAKISTAN

SHAHINA QURESHI M.D, JAVAID SAEED M.B.B.S., CHILDREN HOSPITAL, PIMS, ISLAMABAD.

Malignant lymphomas are the second most common paediatric malignancies in Pakistan following leukaemias. The frequency of lymphomas seen at Children's Hospital, Islamabad from 1987 to 1995 in children <15 years of age was 20.3 %. 105 had Hodgkin's Disease with a frequency of 11.35%.

OBJECTIVE : A retrospective analysis of all cases was done to show the marked clinico-pathological and epidemiological differences in comparison to developed countries and to determine the effectiveness of the treatment regimen used.

PATIENTS & METHODS . Total of 105 patients were registered with Biopsy proven disease.

RESULTS : Majority of our patients were in the younger age group. Mean age was 7.4 years (range 2-13 years). Male : Female ratio was 6:1.7. Mixed celLularity was the most common histological type occurring in 80.9% of cases. Advanced disease stage III and IV was seen in 55.2%. Treatment was initially with MOPP/ABVD & ACOPP. Later all patients were only treated with CCSG protocol ACOPP due to toxicity with ABVD. 69 patients completed treatment i.e. 64.7% . 68 patients achieved complete remission. Six relapsed, one died of measles after treatment, two patients developed second malignancy. 59 patients are in complete remission i.e. 86.76%. In these patients median duration of DFS in 22 months (range 6 to 86 months).

CONCLUSION : Distribution of histological subtypes in similar to that reported from other developing countries and different from developed nations. Treatment with ACOPP is safe, effective and without toxicity.

O-116

HODGKIN'S DISEASE (HD) IN SOUTHERN AFRICA : EPIDEMIOLOGY AND OUTCOME OF CHLVPP OR MOPP AND/OR ABVD TREATMENT

PB Hesseling, G Wessels, FA van Riet, D van Jaarsveld. Tygerberg Hospital, University of Stellenbosch, South Africa

Introduction: Our multi-ethnic population and use of either ChlVPP or MOPP/ABVD for primary therapy of HD, provided the opportunity to analyse epidemiological characteristics and to compare long term outcome in children treated with ChlVPP or other chemotherapy.

Patients and methods: All 39 children < 15 years treated at Tygerberg Hospital with histologically confirmed HD between 9/73 and 1/96 are included in the analysis. They consisted of 20 coloured (mixed ethnic) and 12 white children from the Cape Province in the RSA, and 7 black children from Namibia. We used Ann Arbor clinical staging. Two early patients were splenectomised. Routine investigations included a blood count, liver function tests, bone marrow examination, Gallium scan and ultrasound (more recently). Primary Rx consisted of 6 courses of ChlVPP or MOPP or ABVD or MOPP/ABVD and 20-30 Gy IF radiotherapy to bulky mediastinal disease. The 19 children treated with ChlVPP and 20 children treated with MOPP and/or ABVD had a comparable stage distribution.

Results: 5% (2) had stage I, 41% (16) stage II, 28% (11) stage III and 26 (10) stage IV disease. Coloured and black children presented with more advanced disease and at a younger median age (124 and 119 months) than white children (147 months). NS histology was most common (59%) in white children, MC (40%) in coloured and LD (43%) in black patients. Kaplan-Meier projected survival for all children was 85% for stage I and II at 10 yrs and 48% for stage III and IV at 10 years. Late relapses occurred. The survival after ChlVPP or MOPP and/or ABVD at 10 yrs was identical at 52%. Five treatment related deaths were caused by septicaemia post splenectomy (2), marrow failure, cor pulmonale after pulmonary TB and AML. 12 children have been treated for tuberculosis since diagnosis. Six children developed varicella and 5 herpes zoster.

Conclusions: The age and histological distribution of HD in coloured and black children from a poor socio-economic background fit epidemiological type I and that of white children type III HD (Correa 1971). ChlVPP Rx gave similar survival to MOPP/ABVD variations. Infections were an important cause of death and morbidity. Late relapses may be reduced by routine low dose involved field radiotherapy.

O-117

HODGKIN'S DISEASE IN CHILDREN: 15 YEARS EXPERIENCE

ANTONELI, CBG*, MOURA, JFB**, CARDOSO, H*, NOVAES, PERS**, TAGAWA, EK**
AC CAMARGO HOSPITAL-SAO PAULO-BRAZIL *PEDIATRIC ONCOLOGY, **RADIATION ONCOLOGY

One hundred thirty eight patients treated in the Ped iatic Department at AC Camargo Hospital from 1980 to 1995 were analyzed. Median age was 9 years old and the male: female ratio was 3:1. Clinical staging alone was performed in 27 patients, as follows: CS I = 5, II = 9, III = 5 and IV = 8. Surgical staging was performed in 111 (64 of them with splenectomy), with the following results: I = 16, II = 34, III = 38, and IV = 23 patients. Histological subgroups were: lymphocyte predominance: 28, mixed cellularity: 61, lymphocyte depletion: 3, nodular sclerosis: 43 and unclassified tumors: 3. Treatment consisted of involved fields radiotherapy with 20 Gy in all patients associated with the following chemotherapeutic schedules: MOPP, MOPP/ABVD, ABVD, OPPA/ABVD or VEEP, according to the protocols used during the period of study. Local relapse occured in 19 patients. One patient presented a second malignancy, an osteogenic sarcoma in the right umerus, on a radiation shadow area, 4 years after having finished treatment. Overall and disease-free survival were 87.6% and 81.9%, respectively. Because of the low median age of our patients, we suggest that the treatment should be selected properly to optimize results and decrease late effects in those with initial stages of disease. Maybe chemotherapy alone, instead of the combination radiotherapy + chemotherapy, could be regarded as a new approach for these patients.

O-118

OUTCOME OF B-CELL LYMPHOMAS TREATED AT TYGERBERG HOSPITAL, REPUBLIC OF SOUTH AFRICA

G WESSELS, PB HESSELING, University of Stellenbosch and Tygerberg Hospital, Cape Town, Republic of South Africa

B-cell lymphomas occur more frequently in Africa than in other continents. Reports from Africa on the long term outcome of these patients are limited. In industrialised countries good results are obtained with the French LMB and German BFM protocols in advanced disease and the less toxic COMP regimen in localised disease. **Aim:** To evaluate the outcome, morbidity and supportive measures in children treated for B-cell lymphomas at a single institution in order to formulate future treatment strategies. **Methods:** A descriptive study of all patients <15 years old with B-cell lymphoma treated at Tygerberg Hospital in the RSA between 1983 and 1996. The Murphy system was used for staging all the lymphomas and those children treated according to the LMB-89 protocol were stratified into 3 treatment groups; A, B and C according to the protocol. Survival in children treated with the LMB-89 and with other protocols were calculated by the method of Kaplan and Meier and compared with the log Rank test. Recorded treatment complications in the two groups such as febrile neutropenia, stomatitis, diarrhoea, protracted vomiting and convulsions, were analysed. Leucovorin rescue in the LMB protocol was given 6 hourly until methotrexate serum levels were <0.2μmol/l. Total parenteral nutrition (TPN) was given if children with grade 3 stomatitis tolerated nasogastric tube feeds badly. **Results:** B-cell lymphomas constituted 70% (41) of 59 non Hodgkin lymphomas treated. There were 0 stage I, 9 (22%) stage II, 21 (51%) stage III and 11 (27%) stage IV tumours. 70% presented with abdominal disease and 16% with tumours of the jaw or orbit. Overall survival was 46%. In the 17 children treated with LMB protocol (3 Group A, 14 Group B, 0 Group C) survival was 100% for the 3 group A patients and 76% for all patients (mean follow up 29 months in survivors). In the 24 children treated with other protocols overall survival was 29% (mean follow up 97 months). Children treated with LMB 89 had more episodes of fever and stomatitis, but other complications were similar in both groups. 60% of all LMB patients received TPN compared to 20% of COMP patients. One patient died of sepsis during induction with the LMB and two during induction with other protocols. **Conclusions**: The LMB-89 protocol improved survival over historical controls (76% vs 29%, p0.008), but needed intensive supportive therapy for those receiving group B treatment. Group A and B treatment regimens of the LMB-89 protocol can be implemented without undue risk of treatment related death if attention is paid to the slow initiation of treatment, adequate hydration is maintained and antibiotic coverage is available. In patients who do not have third space fluid collections the routine monitoring of MTX levels is unnecessary and 7 doses of Leucovorin is recommended when administering $3g/m^2$ of MTX.

O-119

USE OF INTENSIVE CHEMOTHERAPY FOR NON HODGKIN LYMPHOMA IN A DEVELOPING COUNTRY

C Mpofu MRCP (UK) and T Revesz MD PhD
Tawam Hospital and UAE University, Al Ain, United Arab Emirates.

Objective To evaluate the results of treating non Hodgkin lymphoma (NHL) with intensive chemotherapy in a developing country.

Method Chart review of all children treated at Tawam Hospital for NHL.

Results 517 children were treated for malignant disease at Tawam Hospital between January 1981 and December 1996. Of these, 44 (8.5%) had NHL. The mean age was 6.2 yr (1.6 - 16.7). Thirty four children had B cell, 9 T cell, and 1 poorly differentiated lymphoma. Twenty one children received relatively mild chemotherapy (NCI 77-04, LSA2L2), while 23 received more intensive chemotherapy (BFM, LMB). The overall 2 yr survival for each group was 63%. Analysis of survival by time period however showed a 2 year survival of 42% in the first 8 yrs (F1), vs 72% in the last 8 yrs (F2). The cause of death in F1 was due to relapsed /progressive disease in 6 cases, and septicaemia in 1. The figures for F2 were 2 and 5 respectively. The deaths in F1 were in consecutive patients in the first 4 yrs. Patient and disease characteristics did not differ significantly in the two groups. There was a total of 14 culture positive septicaemias in 12 patients. Six of these episodes resulted in death, while the others were successfully treated. The organisms included Klebisella(4), Pseudomonas(3), Enterobacter(2), Bacillus(1), and Candida(4).

Conclusion The cure rates of NHL have improved since our unit started looking after children with cancer, and have not been diminished by the introduction of more intensive chemotherapy regimens. However the latter has resulted in a high incidence of serious infections, making supportive care a high priority.

O-120

MANAGEMENT OF NHL IN CHILDREN AT A PEDIATRIC CANCER UNIT FROM A DEVELOPING COUNTRY : EXPERIENCE & LESSONS

Agarwal BR, Gawande Y, Agarwal R, Desai M, Dalvi RB. BJWadia Hospital for Children, Parel, Mumbai - 400 012, India.

Objectives : Over the past few years spectacular progress has been made in the management of childhood NHL with more than 70% overall long term survival rates. In this retrospective study we present our experience with managing childhood NHL. Their clinical characteristics and outcome are highlighted and the lessons for the future discussed.
Methods : 38 consecutive children with NHL seen at a single institution between 1986 to 1996 have been analysed for their clinical features and treatment outcome. Clinical staging for extent of disease and histopathology for morphological classification was carried out on all patients. Immunophenotyping of tumor cells was not available. Children with lymphoblastic lymphoma (LL) were treated with leukemia-like protocols (LSA_2L_2 or UKALLX). COMP therapy was used for patients with non-lymphoblastic lymphomas (NLL) for 18 months. Patients completing induction chemotherapy were evaluable for response.
Results : There were 28 boys and 10 girls in this series. They presented with an abdominal mass (18), mediastinopathy (8) head/neck mass (4) and disseminated disease (8). Only 5 patients had localised NHL while 33 had stage III/IV disease . Histologically 17 had a LL. 8 patients died or opted out before any treatment. 9/30 patients died during induction due to progressive disease (3), neutropenic infection (3) or bleeding (3). 21 patients (70%) completed induction who were considered evaluable for response. The global actuarial survival was 63% at 3 years. 2 cases relapsed, 3 died in remission and 4 were lost to follow up (NED).
Conclusions : A high proportion of cases (31%) were lost either before or after start of treatment. Strategies to reduce this loss are to be developed urgently. Remarkable number of deaths occured during induction chemotherapy, which can be improved by early diagnosis & good supportive care. More aggressive & short length protocols could result in better cure rates, but their use will be limited by resources available for supportive care. Problems of treatment compliance and losses from follow up obviously have to be taken into account when designing new approaches.

O-121

HIV RELATED TUMOURS IN PAEDIATRICS

Thejpal R, Vaithilingum M, Chetty R, Coovadia HM
Department of Paediatrics & Child Health and Anatomical Pathology, University of Natal, Durban, South Africa

Objective: We assessed the impact of the Human Immunodeficiency Virus on paediatric haematological malignancies in South Africa, by comparing the characteristics of patients prior to and during the HIV epidemic.
Method: The study is a prospective study done at the paediatric oncology clinic, King Edward VIII Hospital, Durban. To date we have diagnosed 17 patients with HIV related tumours, recruited from 1990 to September 1996. The spectrum of disease is as follows: leukaemia = 2, Burkitts Lymphoma =2, Non Hodgkin lymphoma =2, 1 undefined abdominal tumour, Kaposi's Sarcoma = 5, mucosal associated lymphoid tissue(MALT) lesions of the parotid gland = 5.

Summary: The latter two categories were diagnosed for the first time in the HIV era. In addition both our non-Burkitts NHL were T-cell as opposed to the frequent occurrence of B cell NHL documented in the literature. The tumours of the parotid gland proved to be both a diagnostic and therapeutic dilemma, because of the spectrum of changes (early myoepithelial sialadenitis, MESA , to low grade malignancy). All 5 of our patients demonstrated histological features qualifying them to be categorised as malignant on light microscopy. However immunohistological studies did not demonstrate the monoclonality of heavy/light chains. Thus we have elected to classify these patients as having MALT lesions. In addition the median age of the patients with HIV related tumours was significantly younger than our uninfected patients, 24 versus 72 months.

Conclusion: Accordingly, it appears that HIV is transforming the profile of childhood cancer in South Africa, bringing with it new diagnostic and therapeutic dilemmas.

O-122

METHOTREXATE IN DOSE OF 1 GR/M^2 IS NOT SAFE FOR HIGH RISK ALL. CHILEAN EXPERIENCE.

M. Campbell, C. Salgado, A. Becker, L. Vargas, J. Quintana on behalf of Chilean National Cooperative Group (PINDA).

ALL Chile 87 multicenter trial was based in ALL BFM 86, but adapted to our possibilities.MTX serum levels were not available so we used MTX 1 gr instead of 5 in protocol M.Leucovorine rescue was adjusted by creatinine clearence. For high risk pts. these were the only differences with ALL BFM 86. The aim of this report is to compare the frequency and site of relapse in both trials, and to relate it with the changes introduced.

Patients and Methods: From June 87 to June 92,425 unselected pts were treated in ALL Chile 87.240 pts. were high risk (risk factor > 0,8, good prednisone response, remission day 33). All received prot I,M (1 gr/m2 x 4), prot II, cranial radiation (12/18 Gy) and maintenance until 2 yrs from diagnosis. 10% of MTX was given in 30 minutes and the remain as a continous infusion over 23,5 hrs. Leucovorine was adjusted by creatinine clearence: ≥ 100 ml/m/1,73 m2=15 mg/m2 iv at hour 48,51,54; < 100=15 mg/m2 at hour 42,45,48,51,54; < 70=50 mg/m2 at hour 42 and 15 mg/m2 at 45,48,51,54. Results were compared, by log rank, to ALL BFM 86 (Blood 84:3122-33,1994).

Results: Remission was obtained in 222/240 (8 early death, 10 LFU). In remission 7 pts died (6 infection, 1 second malignancy). 72 pts relapsed and 143 are free of events, median follow up 6,6 yrs (range 4,6-9,6 yrs).

	ALL CHile 87 n=222	ALL BFM 86 n=606	p (log rank)
BM relapse	50 (22,5%)	89 (14,7%)	< 0.025
CNS relapse	11 (4,9%)	7 (1,1%)	< 0.001
Testes relapse	6 (2,7%)	10 (1,6%)	n.s.
Combined	5 (2,2%)	29 (4,7%)	n.s.
Total relapses	72 (32,4%)	135 (22,1%)	< 0.01

Conclusions: MTX in dose of 1 gr/m2 was enough to prevent testicular relapse in high risk ALL, but it is associated with a significant higher incidence of CNS an BM relapse. This also could be related with the dose of leucovorine used.

O-123

LOW RISK FEBRILE NEUTROPENIA : ALTERNATIVE MANAGEMENT STRATEGY WITH OUTPATIENT ORAL CIPROFLOXACIN

Agarwal BR, Rao N, Desai M, Dalvi RB. Division of Pediatric Hematology/Oncology, B.J.Wadia Hospital for Children, Parel, Mumbai, India.

Objectives: Application of intensive chemotherapy has resulted in significant improvements in the outlook of malignant diseases in children. But fever associated with neutropenia commonly follows such cytotoxic chemotherapy. Prompt administration of intravenous antibiotics after hospitalising children with febrile neutropenia is the standard treatment. In contrast, this study prospectively evaluates outpatient management of febrile neutropenia with oral ciprofloxacin in selected children with "Low Risk" features.

Methods : 74 episodes of febrile neutropenia amongst 28 children with cancer were studied. Children with clinically documented infection were excluded. All episodes were categorized at diagnosis into 2 groups : Low Risk (LR) and High Risk based on the following criteria : (i) patient in disease remission (ii) ANC < 500 /mm^3 and APC > 100 /mm^3 (Absolute Phagocyte Count) (iii) clinically 'well' looking child with no comorbidity (iv) ANC expected to rise within 5 days. Episodes of febrile neutropenia with "Low Risk" were treated randomly with either oral ciprofloxacin (20 mg/kg/d) on outpatient basis or with IV Ciprofloxacin after hospitalisation. They were closely followed daily. Children with high risk episodes were hospitalised and administered IV antibiotics.

Results : 34 episodes were categorised as "Low Risk" at diagnosis amongst 19 children. 18 episodes were treated with oral ciprofloxacin on OPD basis (LR-Group 1), while 16 episodes were treated with IV ciprofloxacin after hospitalising the patients (LR-Group 2). 83% in LR-Group 1 were afebrile at 72 hours with 39% still having or persistently low ANC. The results were comparable in LR-Group 2 patients. Only 2/18 patients required change of antibiotics in LR-Group 1, while 3/16 in LR-Group 2. Significantly, all children with APC > 200 /mm^3 at the time of diagnosis were afebrile at 72 hours irrespective of the treatment arm.

Conclusion : Patients with 'Low risk ' febrile neutropenia are an appropriate population where less intensive treatment strategies can be used. They can be safely and effectively managed with outpatient oral Cipro as demonstrated here (especially when APC is > 200 /mm^3 at diagnosis). This strategy has obvious multiple benefits for the pediatric oncologic practice in countries with limited resources e.g. low costs of treatment without hospitalisation, avoidance of nosocomial infections and better compliance of patients with treatment indiscipline.

O-124

EARLY HOSPITAL DISCHARGE OF CHILDREN WITH CANCER AND FEBRILE NEUTROPENIA, IN A DEVELOPING COUNTRY.

J. Tordecilla, M. Campbell, P. Joannon, V. Soto, C. Rizzardini. Dept. of Pediatric Hematology and Oncology, Hospital Roberto del Río, Santiago Chile.

Patients with cancer and febrile neutropenia are hospitalized to receive empiric broad-spectrum antibiotic therapy. Usually it is maintened until the patient is afebrile and recovered from neutropenia. The aim of this study was to identify the patients who can be "safely" early discharged, receiving reduced amount of antibiotics, with a shorter stay at hospital and a lower cost.

Patients and Methods: From April 92 to April 96 all patients with cancer, axilar temperature over 38º C and ANC < 500 x 10^9/l were admitted. They were cultured (blood, urine), had a chest X Ray and started on parenteral antibiotics (Amikacin + Cloxacillin + Cefoperazone). Early discharged was considered if they were afebrile 48 hrs, appeared well, had normal chest X Ray and negative cultures, despite their ANC.

Results: In 32% of the episodes (84/263) the patients were early discharged, with a $\bar{x}$ 4,5 days in hospital, although 51 were still neutropenic, no one required rehospitalization and none of them died. In 15% (40/263) the pts were discharged on oral antibiotics, because of a minor bacterial infection, $\bar{x}$ 6 ds in hospital, 23 still neutropenic, no one was rehospitalized an none died. Early discharge was not feasible in 53% of episodes (139/263) because of bacteremia, neumonia or prolonged fever, they had $\bar{x}$ 10 ds in hospital and 5 pts died.

Conclusion: 47% of selected children with cancer and febrile neutropenia can be "safely" early discharged, in spite of neutropenia, receiving a reduced amount of antibiotics and at a lower cost than our previous experience.

O-125

MALAYSIAN PARENTS' KNOWLEDGE, ATTITUDES AND PERCEPTIONS (KAP) OF CANCER

Ariffin H, deBruyne JA, Ariffin WA, Chan LL, Lam SK, Lin HP
Dept of Pediatrics, University Hospital Kuala Lumpur (UHKL), Malaysia

The Pediatric Unit UHKL is a major pediatric cancer centre in Malaysia and receives patients from all over the country.
Objective: to explore the KAP of parents whose children underwent cancer treatment in the unit.
Methods: by interview conducted Jan- Apr, 1996 on parents of patients; all patients were < 12 yrs and undergoing treatment .
Results: 87 parents (age: 23-62 yrs) were interviewed. All were literate - 17 % had tertiary education. 44% belonged to social classes IV and V. Only 54% of interviewees knew their child's exact diagnosis. 63 % could not name the oral medication their child was on. Only about half knew of possible relapse or late- effects. Not all (96%) realised the seriousness of the disease. 55% felt that inadequate information was given: discouraged by medical jargon, 38% did not read further about the illness. 28% blamed poliutants as the causative factor while some Malays (16%) and Chinese (19%) blamed the diet. Although most (95%) agreed with hospital treatment, 29% sought concurrent traditional treatment. Another 13% sought traditional medicine first, delaying hospitalisation. Surprisingly, only 81% reacted with disbelief and grief when told the diagnosis. Coping was helped mainly by religion (52%) and family (42%). The parents found fear of death (72%) and painful procedures (16%) hardest to cope with. 60% started contraception after knowing the diagnosis.
Conclusion: Malaysian parents had inadequate knowledge regarding their child's cancer. Many sought traditional treatment. Medical staff could do more in helping them to cope.

O-200

ABDOMINAL SONOGRAPHIC FINDINGS AT PRIMARY DIAGNOSIS OF ACUTE LEUKEMIA IN CHILDREN
Comparison with different clinical risk factors

L.M.Sherif*, A.B.Diab*, K.M.Shawky, N.M.Shawky **, U.R.El Safy* And E.R.A.Khalek***
Pediatric Department * Radiology Department **, Zagazig University Zagazig - Egypt

We conducted a prospective study to evaluate the usefulness of abdominal ultrasonography at primary diagnosis of acute leukemia in children. Thirty eight cases with acute leukemia were studied before initiation of chemotherapy. They were 24 cases with Acute Lymphoblastic Leukemia(ALL) and 14 cases with Acute Non Lymphoblastic Leukemia (ANLL).

The presence of abdominal organomegaly and lymphadenopathy in all cases were assessed and compared with immunophenotype, age groups and white cell (WBC) counts as well as the clinical findings of organomegaly.

Patients with higher WBCs count > 50/microL had significantly more hepatomegaly and splenomegaly (18 cases). The echogenicity of both kidneys was high in most of these children. Children with a higher WBC counts showed intra-abdominal pathology, while those with low counts had normal scans. Lymphadenopathy was found significantly more often in children with T-cell Leukemia (6cases), 4 patients showed large mediastinal lymphadenopathy and 2 cases showed multiple porta-Hepatis lymphadenopathy. Ultrasound revealed the presence of hepatomegaly in 2 patients who were assessed clinically as normal.

In conclusion, our data suggest that abdominal ultrasonography is a useful tool for evaluating children with acute leukemia. Ultrasonography may be recommended for monitoring the response of acute leukemia and status of viscera throughout the disease.

O-126

SOCIAL TRANSITION AND THE IMPACT ON THE DELIVERY OF ONCOLOGY TREATMENT

Strahlendorf C, Wainwright L, Poyiadjis S, Zambakides A.
Paediatric Haematology Oncology Unit, Baragwanath Hospital Soweto, University of the Witwatersrand, South Africa.

South Africa has undergone enormous political, human rights and social changes and the health care structures that exist are still influenced by the legacy of apartheid. Baragwanath Hospital, the largest hospital in the world (3,294 beds) is a tertiary care hospital admitting predominantly black patients from a large catchment area and neighbouring countries (Mozambique, Botswana, Angola). Patients come from under-serviced rural areas, have large families, poor financial resources and compliance difficulties. As a result patients remain in-patients for prolonged periods of time and have little family contact. Social ills such as illiteracy, unemployment, poor housing and sanitation make understanding of disease, treatment and home support for the child difficult. Cultural beliefs also play a role in the acceptance of traditional western health. We administered a questionnaire, addressing the demographics, social support and perceptions of illness of the families admitted to the Paediatric Haematology/Oncology Unit at Baragwanath Hospital. With the information obtained we hope to.

1) Develop better culturally acceptable and educational appropriate counselling.
2) Re-think the delivery of health care.
3) Appreciate financial difficulties and aid in different ways.
4) Establish better transport systems between local, regional and referral hospitals.
5) Change the traditional western paradigm of oncology care.

O-127

TREATMENT OF WILMS' TUMOR WITHOUT RADIOTHERAPY IN NICARAGUA

[1]F.Baez, [2]F.Fossati-Bellani, [1]E.Ocampo, [3]V.Conter, [3]L.Riva, [1]A.Malta, [3]A.Flores, [3]C.Pacheco, [3]P.Lanfranco, [3]A.Sala, [3]G.Fontana, [3]A.Biondi, [3]D.Silvestri, [3]G.Masera, [4]F.Cavalli, [4]C.Sessa. Departments of Oncology of [1]Managua, [2]Milano, [3]Monza and [4]Bellinzona.

Objective To provide information on Wilms' tumor in low income countries. The experience of the "La Mascota" Hospital, Managua, Nicaragua, (made possible by an intenational cooperation program), on treatment of Wilms' tumors without radiotherapy is reported.
Methods 37 pts (22 M, 15 F; mean age 3.2 y, range 0.8-8 yrs) have been diagnosed and treated at "La Mascota" Hospital in the period 1990-1996. Pts were evaluated at the diagnosis with abdominal ultrasound scan and chest X-ray only. Due to organizational problems, a correct pathological staging classification could not be performed. Four pts underwent surgery at the diagnosis (Group A); 27 pts were given preoperative chemotherapy due to the large size of the tumor (Group B); 5 pts were classified as stage IV and 1as stage V, because of metastatic or bilateral disease respectively (Group C). Group A received VCR (1.5 mg/sqm) +ACTD (20 mcg/Kg) weekly x 8 and q 2 wks x 8 thereafter; Groups B and C received VCR+ACTD preoperatively, 4 weekly doses; thereafter VCR+ACTD weekly x 8 (phase 1) and VCR+ACTD alternated to VCR+ACTD+ADM (30 mg/sqm) every 2 weeks x 8 (phase 2) and every 4 weeks x 10 (phase 3) were administered. Radiotherapy was not given since no radiation sources were available in the Country.
Results Of the 37 pts, 29 presented with favorable histology (12 blastematous, 9 trifasic, 1 stromal, 7 epitelioid); 6 pts (Group B) presented with unfavorauble histology (2 anaplastic, 4 rabdoid); in 2 pts histologycal subtype was not determined. No pt presented intraoperative tumor ruptures. 3/4 pts of Group A are off-therapy (OT), without evidence of disease and 1 was lost to follow-up during treatment. Of the 27 pts of Group B, 7 are on therapy; 14 are OT, without evidence of disease; 3 were lost to follow-up during treatment; 3 relapsed (2 in the nodes and 1 in the primary site+lungs). Of the 6 pts of Group C, 2 are on therapy; 2 are OT without evidence of disease; 2 died during treatment. The 3 yrs EFS (±SE) for the whole group is 85.4% (±7) with a median follow-up time of 2.4 yrs (range 1m-6.4 yrs).
Conclusions This experience, although based on a limited number of pts and a short follow-up, suggests that preoperative chemotherapy is useful to avoid tumor ruptures and that satisfactory results can be achieved despite the absence of radiotherapy in the treatment of unstaged pts with Wilms' tumor in low income countries.

O-128

TREATMENT OF ADVANCED RHABDOMYOSARCOMA WITH INTENSIFIED THERAPY.

Strahlendorf C, Wainwright L, Poole J, Poyiadjis S.
Paediatric Haematology Oncology Unit,Baragwanath Hospital, Soweto, University of the Witwatersrand, South Africa.

Background. At Baragwanath Hospital, Soweto, South Africa, the treatment of Rhabdomyosarcoma (RMS) has traditionally been IRS based. With financial restraints and primary health care focus, the treatment of advanced solid tumours has needed to be addressed.
Method. We retrospectively reviewed all patients diagnosed with RMS from 1989-96 at Baragwanath Hospital, to determine the outcome and then propose an alternative therapeutic option. The objectives being to improve DFS, shorten hospitalization and improve health delivery.
Results. 53 patients were diagnosed from 1989-96 with a mean age of 6 years (range 4mo-16yrs) and the M:F ratio of 1.5:1. 25% arose from the H & N, 19% extremities, 17% orbit and 15% genito-urinary and bladder. Based on IRS staging 7% were Stage 1, 7% Stage 2, 66% Stage 3 and 20% Stage 4. 83% of tumours were of the embryonal histological type. 66% of patients died. 5 early septic deaths and the mean survival of the patients that died was 12,9 mo (± SD 8mo) 28% overall DFS, with 0% Stage 3 with distant nodes and Stage 4 survival with 6% defaulting.
As a result of this review we have proposed that all Stage 4 patients and Stage 3 with distant node involvement receive VICE:VCR (2mg/m^2), ifos (3gr/m^2). Carboplat (500mg/m^2) and Etoposide (150mg/m^2) for 4 cycles followed by local control (RT ± Surgery) followed by 2 further cycles with VICE and then consolidated with megatherapy, (VIC) with PBSC rescue. 4 patients have been enrolled; chemotherapy has been well tolerated (without growth factor support) with good primary and secondary response and good pain control. Follow-up is too early but it has allowed quicker delivery of therapy and more time at home.

O-129

COLLABORATIVE EXPERIENCE FOR THE TREATMENT OF RETINOBLASTOMA (RB) BETWEEN MUSTAPHA HOSPITAL, ALGER AND INSTITUT CURIE, PARIS. PRELIMINARY RESULTS

F.Khelfaoui-Ladraa [1] N. Oussedik [3] D. Benahmed [4] K. Bouzid [4], L. Desjardins [2], E. Quintana [1], J. Michon [1], H. Pacquement [1], J.M. Zucker[1], F. Doz[1]. 1 Pediatric Unit. 2 Ophtalmology, Institut Curie, Paris, France. 3 Ophtalmology Unit, CHU Mustapha. 4 Oncology, Centre Pierre & Marie Curie, Alger, Algérie

Introduction and aim of the study :
Extraocular RB and advanced forms of RB occur more frequently in developing countries, presumably as a consequence of delayed diagnosis. Consequently, these patients (pts) require intensive therapies that include chemotherapy (CT) and radiotherapy (RT). Conservative approach is not feasible in Algeria. The two main difficulties in the management of RB are : 1 - to screen RB at an earlier stage
2 - to appropriately select the pts who would benefit from referral in a highly specialized onco-ophtalmology team, despite economical and psychosocial costs. Until 1993, pts were referred for conservative treatment and/or adjuvant CT. Since 1994, only pts for conservative treatment were referred. The aim of our retrospective study is to compare the two therapeutic approaches.
Pts and methods : From 1989 to 1996, 113 pts were treated. Age at diagnosis was 4 months (m) to 6.5 years (y). There were 67 males and 46 females. 1/3 had bilateral disease. The Reese-Ellsworth group was V in almost cases. RB was metastatic at diagnosis in 4 pts and 10 pts had an orbital involvement. Follow-up was 1 m to 4.3 y. Treatment included enucleation (123 eyes), external beam RT (37 pts), adjuvant CT alone (7 pts), RT+ CT (29 pts) and exenteration (17 pts). 79 pts were treated before 93 and 34 pts between 1994 and 1996.
Results : From the 34 pts treated over the second period, 23 are alive without disease with a follow-up of 2 m to 2 y. 8 pts died : progressive disease (3), CNS involvement (1), CT-related toxicity (4). 6/34 pts are lost to follow-up. Overall survival and disease free in the two subgroups of pts (two periods) will be presented at the meeting.
Conclusions :
1- The new therapeutic approach appears to be rational. Since the Pts are frequently referred for conservative treatment after a long time due to the administrative delay, adjuvant CT after enucleation given in Algiers can prevent metastatic disease and may also improve the fellow eye in bilateral cases before referral.
2- However an adequate supportive care in pts with CT and a better families' education are necessary to improve the prognosis of the disease.

O-130

THE TREATMENT OF CRANIOPHARYNGIOMA

Derek Jenkin, Yasser Khafaga, Alan Gray. King Faisal Specialist Hospital, Riyadh, Saudi Arabia.

Purpose: To evaluate the treatment of craniopharyngioma, on a national scale, in a tertiary care facility.
Material & Methods: From 1973-96, 56 consecutive children, less than 18 years old at diagnosis, with craniopharyngioma were actively treated at KFSH, including 44 who were referred for initial definitive resection. Overall treatment policy was to achieve total resection, with more than one resection if necessary, and to irradiate when resection failed. The 44 definitively resected patients are the subject of this report. Advanced disease at diagnosis was common: 15% were blind and 20% had major bilateral visual loss; 46% required endocrine replacement therapy at diagnosis, DDAVP 41%, thyroid 27% and cortisone 20%. Maximum tumour diameter was 0-10 (median 4) cm. The initial definitive resection was total 17 (39%), subtotal 17 (39%) and partial 10 (23%).
Results: For patients who underwent definitive resection at KFSH (n=44), the overall ten year survival was 65% and event-free survival 29%. The cause of death was postoperative 9 (20%); "sudden" at home during first remission 2 (5%); and delayed operative morbidity 1 (2%). No patient has died to date of progressive disease. Of 37 children who survived the first resection 21 have progressed, of whom11 have progressed a second time. Three-year survival, event-free survival and progression/relapse-free survival after total resection was 61%, 48% and 74% and after sub total resection 81%, 31% and 35%. Among the 56 patients actively treated at KFSH 16 received radiation treatment, either electively at diagnosis (4 subtotal, 8 partial resection) or following first progression/relapse (n=4). The three year progression/relapse-free survival for these patients measured from diagnosis or from the date of first relapse was 85%.
Conclusion: Complete resection may cure a child with craniopharyngioma, but the operative mortality and morbidity make this the preferred treatment only for selected patients with low mortality/morbidity risk factors.
Subtotal resection is usually followed by disease progression.
Radiation treatment following the first or second surgical procedure gave encouraging results and should be given routinely after subtotal or lesser resection at diagnosis.

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PEDIATRIC CANCER IN GUATEMALA: A RETROSPECTIVE STUDY.

S. Luna-Fineman, K. Slowing*, P. Valverde*, F. Antillon*, J. Challinor
University of California, San Francisco, CA, USA; *Guatemala

Guatemala is a developing country in which 40% the population is less than 18 years of age. Little is known about the distribution of pediatric cancer. We performed a 4 year retrospective study of all the cases of cancer in children less than 14 years of age. The data was extracted from records of the two major medical

centers in the capital of Guatemala (the only centers where children are treated for cancer). A total of 430 cases were accrued. Fifty-seven percent (245) were male and 43% (185) were female. Forty-eight percent were less than 5 years of age. The patients originated mostly from Guatemala City (39%) and other states (61%). Referrals were highest in the most densely populated states. Acute leukemia was the most common diagnosis (48%); 80% were lymphoid and 20% myeloid. These were followed by Hodgkin's disease (15%), retinoblastoma (9%), brain tumors (8%) and Wilm's tumor (5%). No patient was treated on an established prospective protocol. Complications during therapy were not reported. Although 80% of the general pediatric population in Guatemala are malnourished; malnutrition was documented in only 21% of the cancer patients. Forty-two percent of the patients are reported to be alive at 3 years (28% CR, 11% PR and 5% PD); 16% are dead. The most frequent cause of death was relapse (84%); 16% died of complications of treatment. Most importantly, 41% of the patients were lost to follow-up (13% abandoned treatment against medical advise and 28% did not return to their appointments). The distribution of pediatric cancer differs significantly from that of developed countries. The EFS (28%) is very poor. Abandonment of therapy (41%) is the most important cause of failure. A centralized multidisciplinary pediatric cancer center that provides diagnosis, treatment, support, and education needs to be implemented to improve outcome.

O-132

ROLE OF RADIATION THERAPY IN PEDIATRIC ONCOLOGY IN DEVELOPING COUNTRIES

Kouie Jean Plo, M.D., Department of Radiation Oncology, University of Pennsylvania, Philadelphia, USA

The prognosis for children with cancer in developed countries has improved dramatically in the last four decades, largely because of improved chemotherapy and diagnostic aids. The benefits of these advances, which are costly, are mostly not available to children in emerging nations, who constitute the vastly greater proportion of the world pediatric population. The problems of expense are compounded by social, religious and psychologic factors that often result in poor maintenance treatments and follow-up. This often results in premature termination of postoperative therapy after only a few cycles of chemotherapy. These complex factors can be offset in part by consolidating with postoperative radiotherapy (RT) the gains obtained by surgery and even abbreviated chemotherapy. Postoperative RT thus would be used almost routinely, as it once was before chemotherapy became available, and can be given while the child is still under clinical supervision in the postoperative period. It would be coupled with courses of chemotherapy, using effective drugs that might not be ideal but are less expensive and therefore available. Sponsored by the American Society of Hematology/Oncology and the International Society of Pediatric Oncology, treatment regimens incorporating these concepts are under development for each of the solid tumors of childhood. For instance, preoperative dactinomycin (AMD) and vincristine (VCR) would be used in all Wilms tumor patients, with (1) RT given to all and, (2) doxorubicin added to AMD + VCR for all stages except SIOP Stage I. This seeming overtreatment is designed to "cover" for possible inaccuracies in diagnosis and incomplete chemotherapy.

O-133

SINGLE MODALITY TREATMENT IN HODGKINS DISEASE.
SURVIVAL, SECOND MALIGNANCY AND SALVAGE.

M. Radford and A. Barrett for the UKCCSG

Survival in Hodgkins disease is sufficiently good that the major factor influencing treatment decisions is the incidence of long term toxicity. Second malignancies are of special concern and are clearly related to therapy. We have attempted to minimise toxicity by avoiding combined modality treatment when possible.

Method: 370 patients were entered on study from 1982-1992. Clinical Stage I patients received I.F.R.T. 35Gy. Stage I relapse was treated with chemotherapy. Clinical Stage II-IV patients were treated with ChlVPP chemotherapy. Those with large mediastinal masses also received mediastinal irradiation. Second malignancy rate and progress of relapsing patients was documented.

Results:

Stage	n	10 year Survival %
I	110	96
II	139	92
III	75	85
IV	43	68

Second malignancy rate %

	5 year	10 year
Leukaemia/NHL	0.9	2.7
Solid tumours	0.7	0.7
All S.M.N.	1.7	3.4

Salvage following relapse Stage II-IV

43 patients relapsed and were re-treated
26 remain alive with no evidence of disease.

Conclusion:

Single modality treatment is appropriate for most patients with Hodgkins disease. Nearly two thirds of relapsing patients remain curable. Second malignancy rates are slightly lower than in a previous major study.

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Individualisation of radiation fields based on modern sectional imaging within combination treatment of pediatric Hodgkin's Disease based on the experience from the German-Austrian multicentre trial (HD-90)

R.Pötter, K. Dieckmann, J. Hofmann, U. Haverkamp (2), A. Drochtert (2), F.J. Pratt (1), W. Wagner (3), G. Schellong (4)
Universitätsklinik für Strahlentherapie und Strahlenbiologie, AKH Wien, Austria;
Universität Clemenshospital Münster (1,2), Germany, Osnabrück (3); German-Austrian trial centre for Hodgkin's Disease, Universität Münster, Germany (4)

Purpose: Definition of the supradiaphragmatic involved lymph node area to be irradiated within combinded modality treatmant of pediatric Hodgkin's Disease (HD) based on clinical examination and modern sectional imaging (CT/US).

Material and Methods: From October 1990 to July 1994 447 patients have been enrolled in the German-Austrian multicentre pediatric HD-study (HD 90) with 73 centres participating. For each of these patients the individual spread of disease at diagnosis was documented based on the documentation forms. A central review of chest X-ray films, chest CT, and abdominal CT was performed. In individual proposal for the radiation field was set up and sent to the respective centre. The radiation fields proposed were compared to the classical IF-radiotherapy for 386 patients with supradiaphragmatic disease.

Results: The individualisation of the classical IF-radiotherapy led to changes in altogether 182/386 patients (47%). In neck involvement (n=311), in mediastinal involvement (n=335), and in comined involvement of mediastinum and neck (n=260), the changes were in 112 pats (36%), in 70 pats (21%), and in 140 pats (54%) respectively. 175/182 changes were volume reduction. For the neck and the mediastinum typical patterns of spread resulting in modified IF-radiotherapy could be identified: upper neck; lower neck including the supraclavicular region; upper mediastinum including the thoracic aperture; upper mediastinum including bilateral hili, whole mediastinum. The proposed radiation fields were in 95% a combination of one or more of these areas. Analysis of recurrence (n=21) revealed no recurrence in a lymph node area treated by a modified radiation field.

Conclusion: Classical IF-radiotherapy for supradiaphragmatic pediatric HD can be modified based on modern sectional imaging in almost half of the patients resulting in individualized radiation fields covering the involved lymph node areas. These changes (volume reduction) do not jeopardize local control within effective combination treatment.